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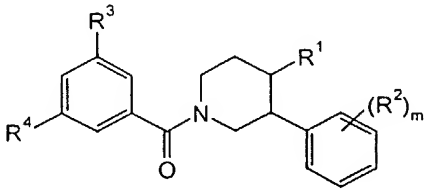
(54) Title: PIPERIDINE DERIVATIVES AS NEUROKININ 1 ANTAGONISTS

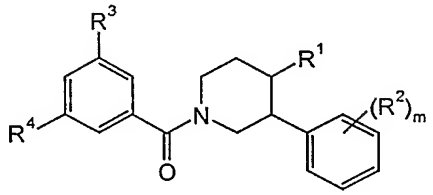



( I )

(57) Abstract: The invention relates to compounds of the general formula, wherein $R^1$ is optionally substituted phenyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl or is thiomorpholinyl, 1-oxo-thiomorpholinyl or 1,1-dioxothiomorpholinyl. These compounds have a good affinity to the NK-1 receptor and they are therefore suitable in the control or treatment of diseases, related to this receptor.

# PIPERIDINE DERIVATIVES AS NEUROKININ 1 ANTAGONISTS

The present invention relates to compounds of the general formula



I

wherein

$R^1$ a) is phenyl, unsubstituted or substituted by one or more substituents selected from the group $R^{1'}$ consisting of
- halogen,
- trifluoromethyl,
- piperazinyl, optionally substituted by lower alkyl,
- morpholinyl,
- NH-phenyl,
- pyrrolidinyl,
- $NH(CH_2)_n$-O-lower alkyl,
- $NR_2$,
- $NH(CH_2)_n$-cycloalkyl,
- $NH(CH_2)_n$-$NR_2$, or is

b) morpholinyl, optionally substituted by one or two lower alkyl groups, or is

c) piperazinyl, unsubstituted or substituted in the 4-position by the group $R^{1''}$which is
- lower alkyl,
- cycloalkyl,
- phenyl,
- benzoxazolyl,
- pyridinyl,
- pyrimidinyl
- pyrazinyl,
- $(CH_2)_n$-cycloalkyl,
- $(CH_2)_n$-phenyl,

- $(CH_2)_n$-hydroxy,
- $(CH_2)_n$-$CF_3$,
- $(CH_2)_n$-C(O)-morpholinyl,
- $(CH_2)_n$-C(O)-N(R)-phenyl, wherein the phenyl ring is optionally substituted by lower alkyl or halogen,
- $(CH_2)_n$-C(O)-$NR_2$,
- C(O)-phenyl, wherein the phenyl ring is optionally substituted by trifluoromethyl,
- C(O)-$(CH_2)_n$-phenyl,
- C(O)-$NR_2$,
- C(O)-NR-$(CHR)_n$-phenyl,
- C(O)-lower alkyl,
- C(O)-$CF_3$,
- C(O)-cycloalkyl,
- C(O)-morpholinyl,
- C(O)O-lower alkyl,
- C(O)-O-$(CH_2)_n$-$NR_2$,
- $S(O)_2$-lower alkyl,

or is

d) pyrrolidinyl, optionally substituted by one or more groups $R^{1'''}$, which are

- halogen,
- hydroxy,
- =O,
- $NR_2$,
- N(cycloalkyl)$_2$,
- N[$(CH_2)_n$cycloalkyl]$_2$,
- NR-C(O)-cycloalkyl,
- O-$(CH_2)_n$-cycloalkyl, or is

e) piperidinyl, optionally sbstituted by one or more groups $R^{1''''}$ in the 3 or 4-position, which groups are

- hydroxy,
- =O,
- halogen,
- morpholinyl,
- $NR_2$,
- NR-cycloalkyl,
- NR-C(O)-cycloalkyl,
- NR-C(O)-phenyl,
- NR-C(O)-$(CH_2)_n$-phenyl,

- O-$(CH_2)_n$-cycloalkyl,

or is

f) thiomorpholinyl, 1-oxo-thiomorpholinyl or 1,1-dioxothiomorpholinyl;

$R^2$ is independently from "m" hydrogen, halogen, lower alkyl, -NH-$(CH_2)_n$-O-lower alkyl, pyrrolidinyl or morpholinyl;

$R^3/R^4$ are independently from each other trifluoromethyl or halogen;

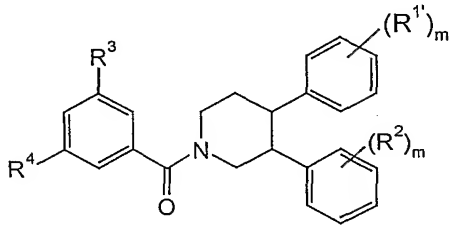
R is hydrogen or lower alkyl and may be the same or different in case of $R_2$;

n is 1, 2, 3 or 4;

m is 0, 1 or 2;

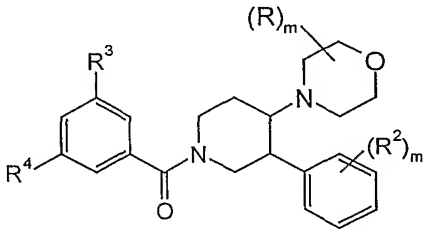
and to pharmaceutically acceptable acid addition salts thereof.

In more detail, the compounds of the present invention relate to formulas



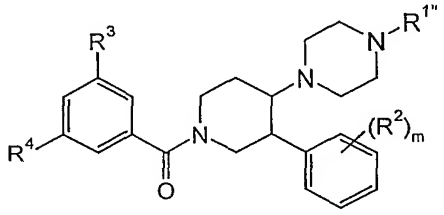
1A,

wherein m is 0, 1 or 2 and $R^{1'}$, $R^2$, $R^3$ and $R^4$ are described above, or to



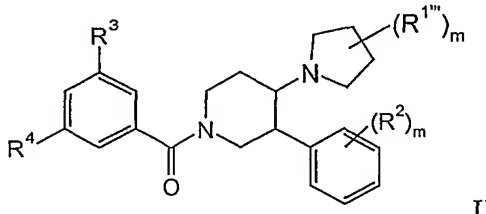
IB,

wherein R is lower alkyl, m is 0, 1 or 2, $R^2$, $R^3$ and $R^4$ have the significances given above, or to



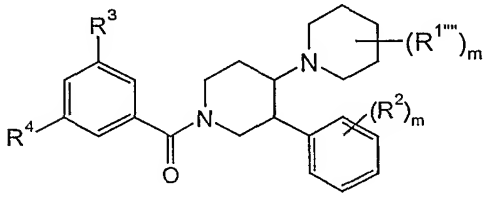
IC,

wherein m is 0, 1 or 2, $R^{1''}$, $R^2$, $R^3$ and $R^4$ have the significances given above, or to



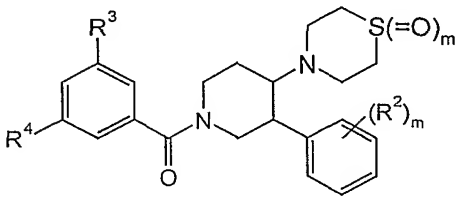
ID,

wherein m is 0, 1 or 2, $R^{1'''}$, $R^2$, $R^3$ and $R^4$ have the significances given above, or to



IE,

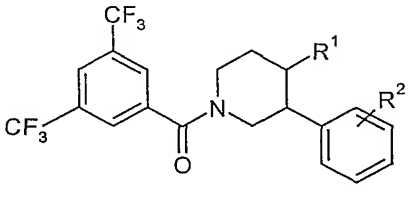
wherein m is 0, 1 or 2, $R^{1''''}$, $R^2$, $R^3$ and $R^4$ have the significances given above, or to



1F

wherein $R^2$, $R^3$ and $R^4$ are described above and m is 0, 1 or 2.

Further encompassed by the present invention are compounds having the formula



I-1

wherein

$R^1$ is phenyl, unsubstituted or substituted by one or two substituents, selected from the group $R^{1'}$, consisting of

- halogen,
- trifluoromethyl,
- piperazinyl, optionally substituted by lower alkyl,

- morpholinyl,
- NH-phenyl,
- pyrrolidinyl,
- $NH(CH_2)_n$-O-lower alkyl,
- $NR_2$,
- $NH(CH_2)_n$-cycloalkyl,
- $NH(CH_2)_n$-$NR_2$, or is

morpholinyl, or is

piperazinyl, unsubstituted or substituted by the group $R^{1"}$, which is

- lower alkyl,
- cycloalkyl,
- C(O)-phenyl, wherein the phenyl ring is optionally substituted by
  - trifluoromethyl,
- $(CH_2)_n$-C(O)-$NR_2$,
- $(CH_2)_n$-cycloalkyl,
- $(CH_2)_n$-phenyl,
- C(O)-lower alkyl,
- C(O)-$CF_3$,
- C(O)-cycloalkyl,
- C(O)-morpholinyl,
- C(O)-O-$(CH_2)_n$-$NR_2$,
- $(CH_2)_n$-C(O)-N(R)-phenyl, wherein the phenyl ring is optionally substituted by lower alkyl,
- pyrazinyl, or is

pyrrolidinyl, optionally substituted by the group $R^{1'''}$, which is

- hydroxy,
- =O,
- O-$(CH_2)_n$-cycloalkyl, or is

piperidinyl, optionally sbstituted by the group $R^{1''''}$, which is

- hydroxy,
- O-$(CH_2)_n$-cycloalkyl,
- =O,
- halogen, or is

thiomorpholinyl, 1-oxo-thiomorpholinyl or 1,1-dioxothiomorpholinyl;

$R^2$ is hydrogen, halogen, lower alkyl, -NH-$(CH_2)_n$-O-lower alkyl, pyrrolidinyl or morholinyl;

R is hydrogen or lower alkyl and may be the same or different in case of $R_2$; and

n is 1, 2, 3 or 4;

and pharmaceutically acceptable acid addition salts thereof.

The compounds of formula I and their salts are characterized by valuable therapeutic properties. It has been surprisingly found that the compounds of the present invention are antagonists of the Neurokinin 1 (NK-1, substance P) receptor. Substance P is a naturally occurring undecapeptide belonging to the tachykinin family of peptides, the latter being so-named because of their prompt contractile action on extravascular smooth muscle tissue. The receptor for substance P is a member of the superfamily of G protein-coupled receptors.

The neuropeptide receptor for substance P (NK-1) is widely distributed throughout the mammalian nervous system (especially brain and spinal ganglia), the circulatory system and peripheral tissues (especially the duodenum and jejunum) and are involved in regulating a number of diverse biological processes.
The central and peripheral actions of the mammalian tachykinin substance P have been associated with numerous inflammatory conditions including migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease as well as mediation of the emetic reflex and the modulation of central nervous system (CNS) disorders such as Parkinson's disease (Neurosci. Res., 1996, 7, 187-214), anxiety (Can. J. Phys., 1997, 75, 612-621) and depression (Science, 1998, 281, 1640-1645).
Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases reviewed in "Tachykinin Receptor and Tachykinin Receptor Antagonists", J. Auton. Pharmacol., 13, 23-93, 1993.

Furthermore, Neurokinin 1 receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of tachykinin, in particular substance P. Examples of conditions in which substance P has been implicated include disorders of the central nervous system such as anxiety, depression and psychosis (WO 95/16679, WO 95/18124 and WO 95/23798).

The neurokinin-1 receptor antagonists are further useful for the treatment of motion sickness and for treatment induced vomiting.

In addition, in The New England Journal of Medicine, Vol. 340, No. 3 190-195, 1999 has been described the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist.

Furthermore, US 5,972,938 describes a method for treating a psychoimmunologic or a psychosomatic disorder by administration of a tachykinin receptor, such as NK-1 receptor antagonist.

The usefulness of neurokinin 1 receptor antagonists for the treatment of certain forms of urinary incontinence is further described in "Neuropeptides, 32(1), 1-49, (1998)" and "Eur. J. Pharmacol., 383(3), 297-303, (1999)".

The compounds of formula I can also be used in form of their prodrugs. Examples are esters, N-oxides, phosphate esters, glycoamide esters, glyceride conjugates and the like. The prodrugs may add to the value of the present compounds advantages in adsorption, pharmacokinetics in distribution and transport to the brain.

NK1 receptor antagonists have been reported to have also a beneficial effect in the therapy of traumatic brain injury (oral disclosure by Prof. Nimmo at the International Tachykinin Conference 2000 in La Grande Motte, France, October 17-20, 2000 with the title "Neurokinin 1 (NK-1) Receptor Antagonists Improve the Neurological Outcome Following Traumatic Brain Injury" (Authors: A.J. Nimmo, C.J. Bennett, X.Hu, I. Cernak, R. Vink)."

Objects of the present invention are the compounds of formula I and pharmaceutically acceptable salts thereof, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-mentioned compounds in the control or prevention of illnesses, especially of illnesses and disorders of the kind referred to earlier or in the manufacture of corresponding medicaments.
Objects of the present invention are all racemic compounds of formula I, including their corresponding enantiomers. Most of the enantiomers have been separated from their corresponding racemic compounds. It has been shown that the corresponding enantiomers are more active in the test for NK-1 binding as described below.

The preferred stereochemical position is the cis-position.

The most preferred indications in accordance with the present invention are those, which include disorders of the central nervous system, for example the treatment or prevention of certain depressive disorders or emesis by the administration of NK-1 receptor antagonists. A major depressive episode has been defined as being a period of at

least two weeks during which, for most of the day and nearly every day, there is either depressed mood or the loss of interest or pleasure in all, or nearly all activities.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "lower alkyl" denotes a straight- or branched-chain alkyl group containing from 1-7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, t-butyl and the like.
Preferred lower alkyl groups are groups with 1-4 carbon atoms.

The term "lower alkoxy" denotes a group wherein the alkyl residues are as defined above, and which is attached via an oxygen atom.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "cycloalkyl" denotes a saturated carbocyclic group, containing 3-6 carbon atoms.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulfonic acid, p-toluenesulfonic acid and the like.

Exemplary preferred are compounds of formula 1A, in which $R^{1'}$ is hydrogen, bromo, morpholinyl, 4-methyl-piperazinyl or $-NH(CH_2)_2OCH_3$, for example the following compounds:

rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-morpholin-4-yl-phenyl)-3-phenyl-piperidin-1-yl]-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-{4-[4-(4-methyl-piperazin-1-yl)-phenyl]-3-phenyl-piperidin-1-yl}-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-phenyl-piperidin-1-yl]-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(3-bromo-phenyl)-3-phenyl-piperidin-1-yl]-methanone or
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-{4-[4-(2-methoxy-ethylamino)-phenyl]-3-phenyl-piperidin-1-yl}-methanone.

Further preferred are compounds of formula IB, wherein $R^2$ is hydrogen, fluoro or chloro. Examples of such compounds are:

rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-morpholin-4-yl-piperidin-1-yl]-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(4-morpholin-4-yl-3-phenyl-piperidin-1-yl)-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-morpholin-4-yl-piperidin-1-yl]-methanone or
Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-morpholin-4-yl-[1,4']bipiperidinyl-1'-yl]-methanone.

Further preferred are compounds of formula IC, wherein $R^{1"}$ is hydrogen, methyl, $-C(O)CF_3$, $-(CH_2)_2OH$, $-CH_2C(O)N(CH_3)_2$, $CH_2$-cyclopropyl, benzyl, -C(O)-cyclopropyl, -C(O)-morpholinyl, pyrazinyl, cyclopropyl or $-CH_2CONHC_6H_3(CH_3)_2$, $-CH_2CONHC_6H_4F$, $-C(O)CH_2$-phenyl, and $R_2$ is hydrogen, methyl, chloro or fluoro. Examples of such compounds are:

rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-methyl-piperazin-1-yl), -3-phenyl-piperidin-1-yl]-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone,
rac-cis-2 {4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-N,N-dimethyl-acetamide,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropylmethyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone,
rac-cis-[4-(4-benzyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone,
rac-cis-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-morpholin-4-yl-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone,
rac-cis-2-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-N-(2,6-dimethyl-phenyl)-acetamide,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-phenyl-4-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-piperidin-1-yl]-methanone,
(+)-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone,

Rac-cis-2-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-N-(4-fluoro-phenyl)-acetamide,
Rac-cis-1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone,
Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-piperazin-1-yl-piperidin-1-yl]-methanone,
Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropylmethyl-piperazin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[3-phenyl-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone,
(-)-4-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropylmethyl-piperazin-1-yl)-3-p-tolyl-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-3-p-tolyl-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-{4-[4-(morpholine-4-carbonyl)-piperazin-1-yl]-3-p-tolyl-piperidin-1-yl}-methanone,
Rac-cis-1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone,
(-)-1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropyl-piperazin-1-yl)-3-p-tolyl-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-methyl-piperazin-1-yl)-3-p-tolyl-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-(4-cyclopropylmethyl-piperazin-1-yl)-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropylmethyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-3-phenyl-piperidin-1-yl}-methanone or
(-)-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone.

Further preferred are compounds of formula IE, wherein $R^{1''''}$ is fluoro, hydroxy, -NHC(O)-cyclopropyl, -NHC(O)$CH_2$-phenyl, -NH-cyclopropyl,-N$(CH_2)_2$, -O$CH_2$-cyclopropyl or =O and $R^2$ is hydrogen, chloro or fluoro. Examples of such compounds are:

rac-cis- (3,5-bis-trifluoromethyl-phenyl)-(4,4-difluoro-3'-phenyl-[1,4']bipiperidinyl-1'-yl)-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-fluoro-phenyl)-3-hydroxy-[1,4']bipiperidinyl-1'-yl]-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(4-hydroxy-3'-phenyl-[1,4']bipiperidinyl-1'-yl)-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(4-cyclopropylmethoxy-3'-phenyl-[1,4']bipiperidinyl-1'-yl)-methanone,
rac-cis-1'-(3,5-bis-trifluoromethyl-benzoyl)-3'-phenyl-[1,4']bipiperidinyl-4-one,
Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-hydroxy-[1,4']bipiperidinyl-1'-yl]-methanone,
Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-cyclopropylmethoxy-[1,4']bipiperidinyl-1'-yl]-methanone,
(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-cyclopropanecarboxylic acid [1'-(3,5-bis-trifluoromethyl-benzoyl)-3'-(4-fluoro-phenyl)-[1,4']bipiperidinyl-3-yl]-amide,
(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-N-[1'-(3,5-bis-trifluoromethyl-benzoyl)-3'-(4-fluoro-phenyl)-[1,4']bipiperidinyl-3-yl]-2-phenyl-acetamide,
Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-dimethylamino-[1,4']bipiperidinyl-1'-yl]-methanone or
Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-cyclopropylamino-[1,4']bipiperidinyl-1'-yl]-methanone.

Further preferred are compounds of formula ID, wherein $R^{1'''}$ is hydrogen, hydroxy, amino, -$OCH_2$-cyclopropyl or =O and $R^2$ is hydrogen, chloro or fluoro. Examples of such compounds are:

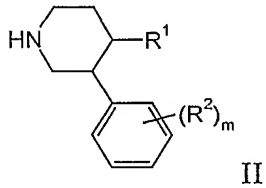
(3R,3'R,4R)- and (3S,3'R,4S)-(3,5-bis-trifluoromethyl-phenyl)-[4-(3'-hydroxy-pyrrolidin-1'-yl)-3-phenyl-piperidin-1-yl]-methanone,
(3R,3'R,4R)- and (3S,3'R,4S)-(3,5-bis-trifluoromethyl-phenyl)-[4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-3-phenyl-piperidin-1-yl]-methanone,
rac-cis-1-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-pyrrolidin-3-one,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-pyrrolidin-1-yl-piperidin-1-yl]-methanone or
(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-[4-(3-amino-pyrrolidin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone.

Further preferred are compounds of formula IF, wherein m is 0, 1 or 2 and $R^2$ is hydrogen. Examples of such compounds are:

rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-thiomorpholin-4-yl-piperidin-1-yl)-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(1-oxo-1l 4-thiomorpholin-4-yl)-3-phenyl-piperidin-1-yl]-methanone or
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(1,1-dioxo-1l 6-thiomorpholin-4-yl)-3-phenyl-piperidin-1-yl]-methanone.

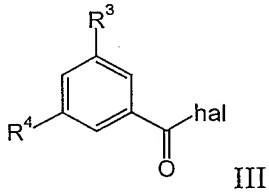
The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

a) reacting a compound of formula



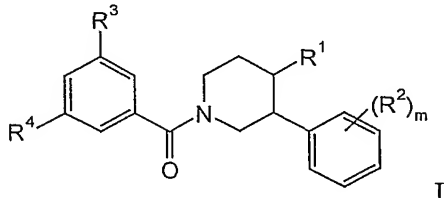
II

with a compound of formula



III

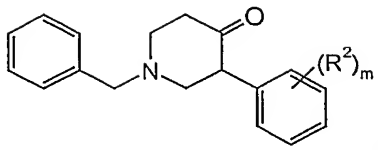
to a compound of formula



I

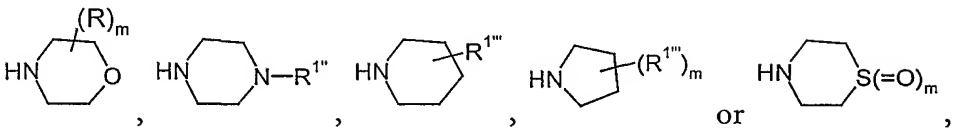
wherein $R^1$ is phenyl, optionally substituted by halogen, $R^2$, $R^3$ and $R^4$ have the significances given above, hal is halogen and m is 0, 1 or 2,
or

b) reacting a compound of formula



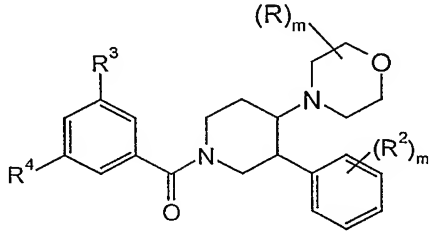
IV

with a compound of formulas



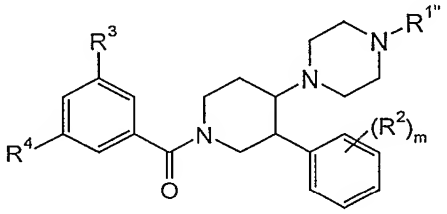
or

debenzylating, and then acylating with a compound of formula III to give a compound of formulas



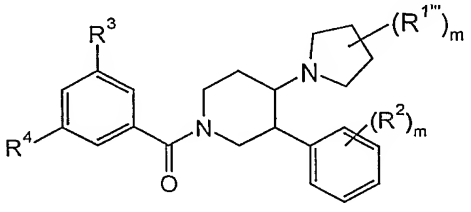
IB,

wherein R, $R^2$, $R^3$, $R^4$ and m have the significances given above, or



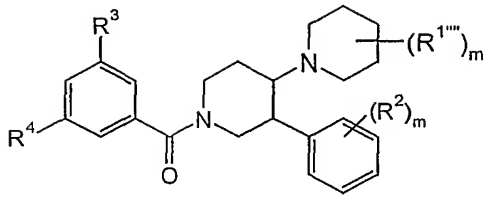
IC,

wherein $R^{1"}$, $R^2$, $R^3$, $R^4$ and m have the significances given above, or



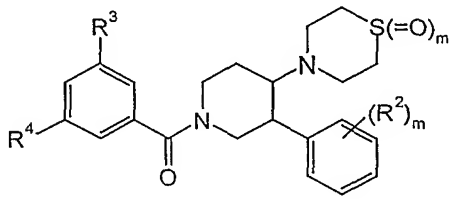
ID,

wherein $R^{1'''}$, $R^2$, $R^3$, $R^4$ and m have the significances given above, or



IE,

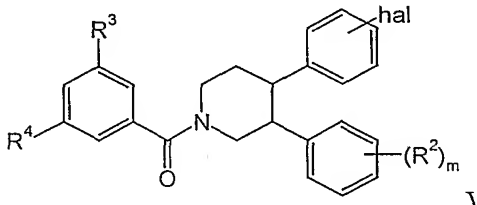
wherein $R^{1''''}$, $R^2$, $R^3$, $R^4$ and m have the significances given above, or



IF

wherein $R^2$, $R^3$, $R^4$ and m have the significances given above, or

c) aminating a compound of formula

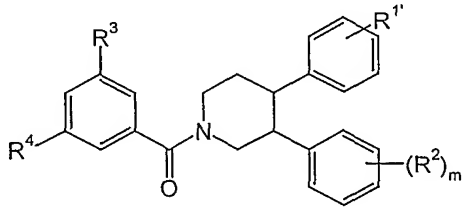


V

with an amine derivative of formula

$R^{1'}H$ VI

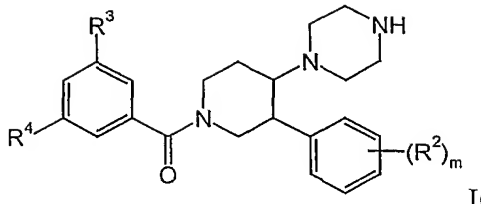
to a compound of formula



IA1

wherein $R^{1'}$ is piperazinyl, optionally substituted by lower alkyl, morpholinyl, -NH-phenyl, pyrrolidinyl, $-NH(CH_2)_n$-O-lower alkyl, $-NR_2$, $-NH(CH_2)_n$-cycloalkyl or $-NH(CH_2)_n-NR_2$, and the definitions of $R^2$, $R^3$ and $R^4$ are given above, or

d) reacting a compound of formula

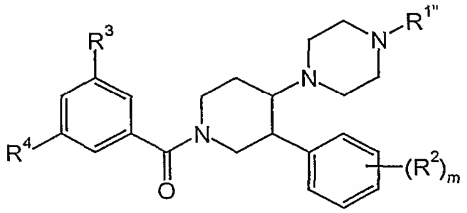


IC1

with a compound of formula

$R^{1"}$hal VII

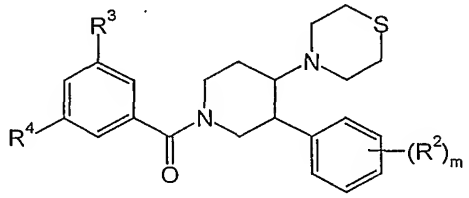
to a compound of formula



IC

wherein the definitions of substituents are given above, or

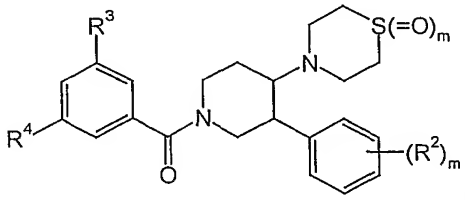
e) oxidizing a compound of formula



IF1

with oxone®

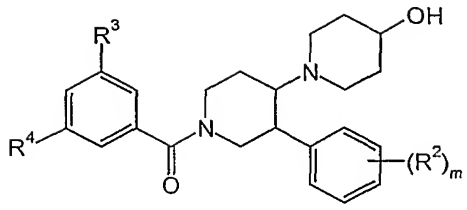
to a compound of formula



IF

wherein m is 1 or 2 and $R^2$, $R^3$ and $R^4$ are described above, or

f) alkylating a compound of formula

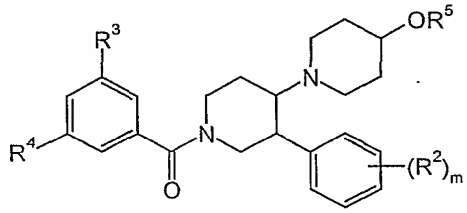


IE1

with a compound of formula

$R^5$hal VIII

to a compound of formula

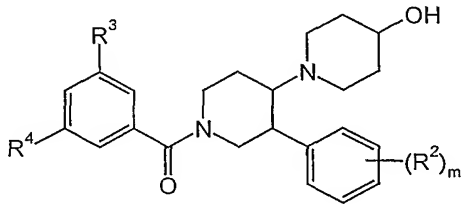


IE2

wherein $R^5$ is $-(CH_2)_n$-cycloalkyl, and $R^2$, $R^3$, $R^4$ and m are described above, or

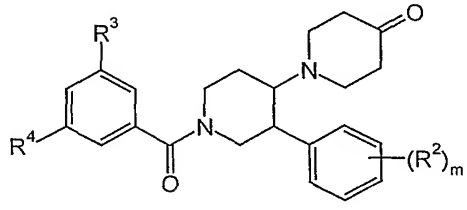
or

g) oxidizing a compound of formula



IE1

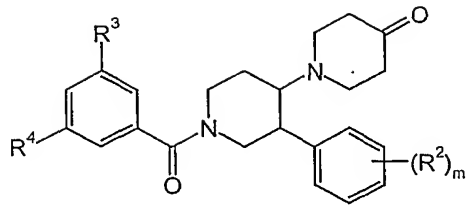
to a compound of formula



IE3

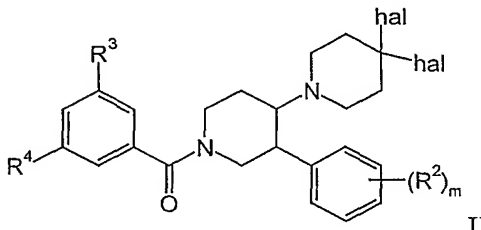
wherein $R^2$, $R^3$, $R^4$ and m are described above, or

h) halogenating a compound of formula



IE3

to a compound of formula



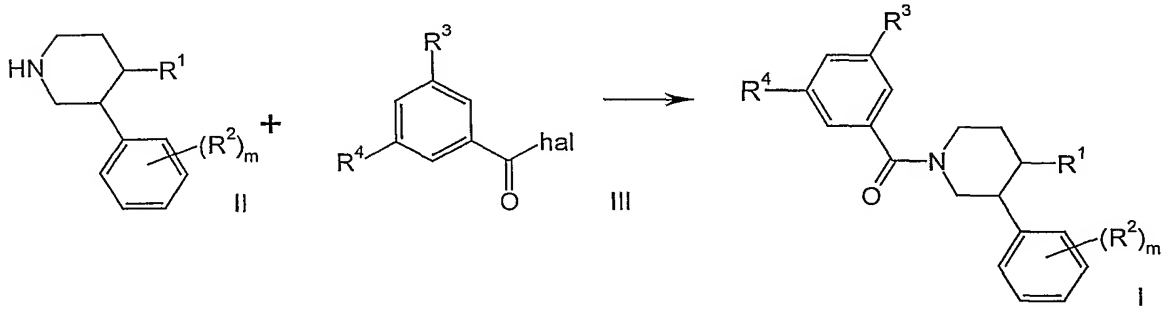
IE4,

and

if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

The following schemes 1-8 and specific examples 1 to 130 describe the processes for preparation of compounds of formula I in more detail. The starting materials are known compounds and may be prepared according to methods known in the art.

Scheme 1

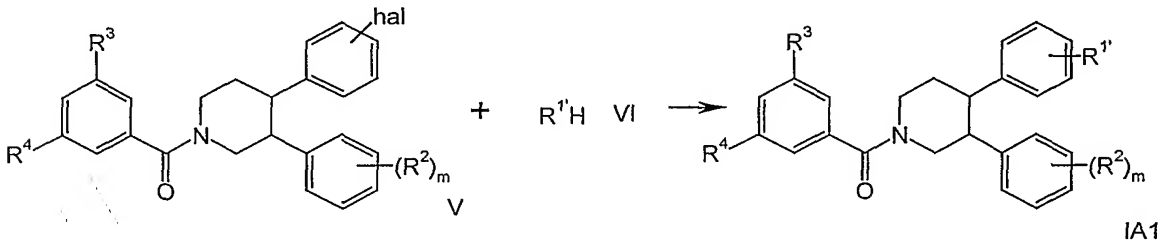


$R^1$ is phenyl, optionally substituted by halogen, $R^2$, $R^3$ and $R^4$ are described above, m is 0, 1 or 2 and hal is chloro or bromo.

Starting materials of formula II or their salts can be obtained according to known procedures (*e.g.* Petit, S.; Nallet, J. P.; Guillard, M.; Dreux, J.; Chermat, R.; Poncelet, M.; Bulach, C.; Simon, P.; Fontaine, C.; et al, Eur. *J. Med. Chem.* 1991, *26*, 19-32).

Compounds of formula I can be obtained by acylation of a compound of formula II with an acid chloride of formula III in the presence of a base, like triethylamine, in an inert solvent like methylene chloride.

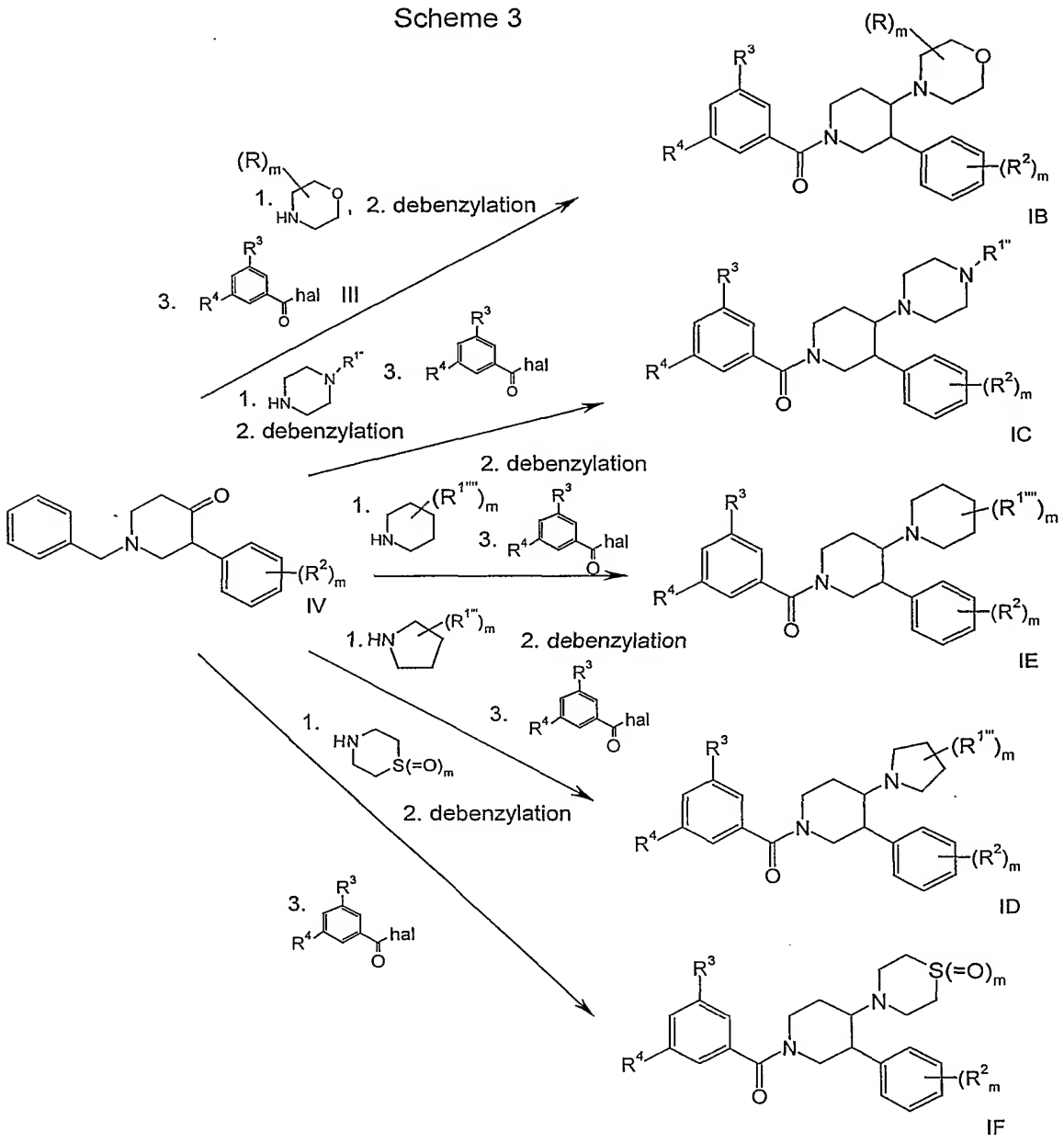
Scheme 2




$R^2$ is described above, m is 0, 1 or 2 and $R^{1'}$ is piperazinyl, optionally substituted by lower alkyl, or is morpholinyl, -NH-phenyl, pyrrolidinyl, $-NH(CH_2)_n$-O-lower alkyl, $-NR_2$, $-NH(CH_2)_n$-cycloalkyl or $-NH(CH_2)_n-NR_2$. Hal is bromo or chloro and m is 0, 1 or 2.

Compounds of formula 1A1 can be obtained by amination of aromatic chlorides or bromides of formula V using an amine of formula VI, like morpholine or N-methylpiperazine, and sodium tert-butoxide, a catalyst like tris(dibenzylideneacetone)dipalladium(0) and a ligand like rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or biphenyl-2-yl-dicyclohexyl-phosphane in an inert solvent like toluene. The method is described in detail in S. Buchwald et al, *J. Am. Chem. Soc.* 1996, *118*, 7215-7218 and *J. Am. Chem. Soc.* 1998, *120*, 9722-9723.

Scheme 3




Starting materials of formula IV can be obtained according to literature procedures (e. g. Lindenmann, Adolf; Suess, Rudolf., CH 545288.)

Compounds of formula IB, IC, ID, IE and IF can be obtained by the following sequence of reactions:

1. Reductive amination of a ketone of formula IV using the cyclic tertiary amine as described in scheme 3, an activating agent like titanium(IV)isopropoxide and a reducing agent, like sodium cyanoborohydride, in a protic solvent like methanol or ethanol, followed by hydrolysis of the intermediate cyanamide, using sodium hydroxide in ethylenglycol for the preparation of compounds of formula IC1.

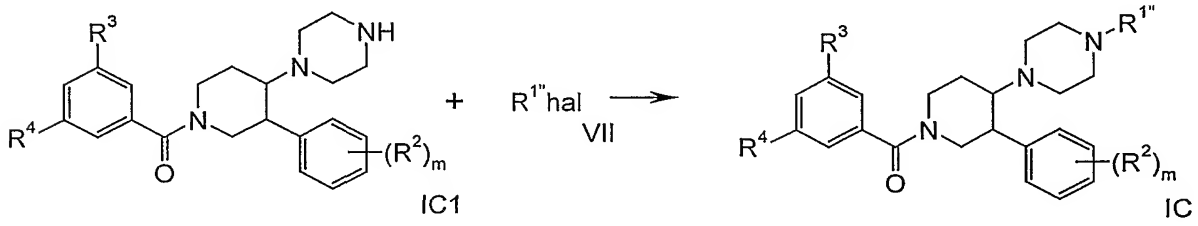
2. Protection of the hydrogen atom on the cyclic amine using trifluoroacetic acid anhydride, 4-dimethylaminopyridine and pyridine in methylene chloride (only for the preparation of compounds of formula IC1).

3. Debenzylation with catalytic amounts of 10 % Pd/C with hydrogen at 1 atm in methanol at acidic pH, or debenzylation using 1-chloroethyl chloroformate in methylene chloride followed by refluxing in methanol.

4. Acylation with an acid chloride of formula III in the presence of a base like triethylamine in an inert solvent like methylene chloride.

5. Deprotection of the trifluoroacetamide using potassium carbonate in a mixture of methanol and water (for the preparation of compounds of formula IC1 only).

Scheme 4



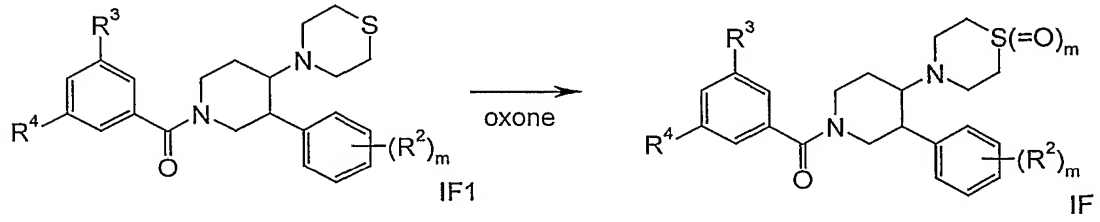

$R^{1"}$, $R^2$, $R^3$ and $R^4$ and m have the significances given above and hal is chloro or bromo. Compounds of formula IC can be obtained by

- alkylating a compound of formula IC1 with an alkyl chloride or alkyl bromide of formula VII in an inert solvent like N,N-dimethylforamide in the presence of a base like potassium carbonate, or

- acylating a compound of formula IC1 with an acid chloride of formula $R^{1"}$ in an inert solvent like methylene chloride in the presence of a base like triethyl amine, or

- treating a compound of formula IC1 with an aromatic bromide or chloride of formula VII at an elavated temperature without any solvent.

Scheme 5

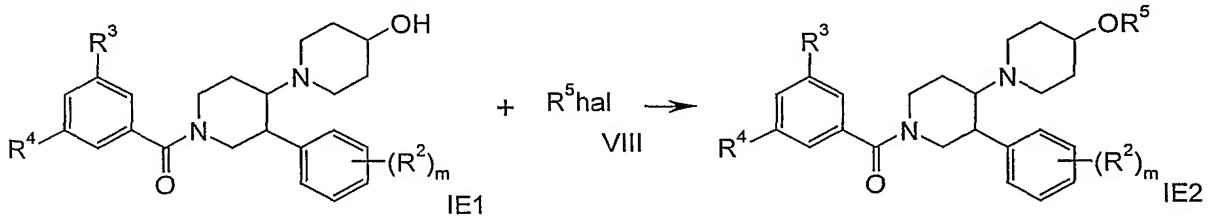


$R^2$, $R^3$ and $R^4$ have the significances given above and m is 1 or 2.

Sulfoxides of formula IF (m=1) can be obtained by treating a thiomorpholine of formula IF1 with 0.6 eq of potassium peroxymonosulfate (Oxone).

Sulfones of formula IF (m=2) can be obtained by treating a thiomorpholine of formula IF1 with an excess of potassium peroxymonosulfate (Oxone).

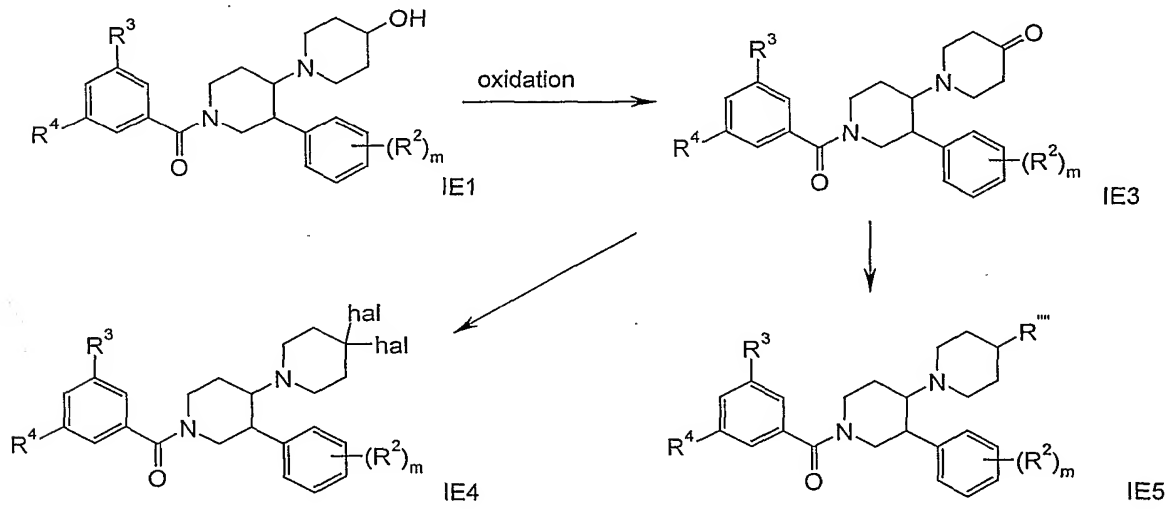
Scheme 6




$R^2$, $R^3$ and $R^4$ have the significances given above and $R^5$ may be, for example, $-(CH_2)_n$-cycloalkyl. Hal is chloro or bromo.

Ethers of formula IE2 can be obtained by treating an alcohol of formula IE1 with a base like sodium hydride and an alkylating agent like an alkyl bromide or alkyl chloride of formula VIII in an inert solvent like dimethylformamide.

Scheme 7

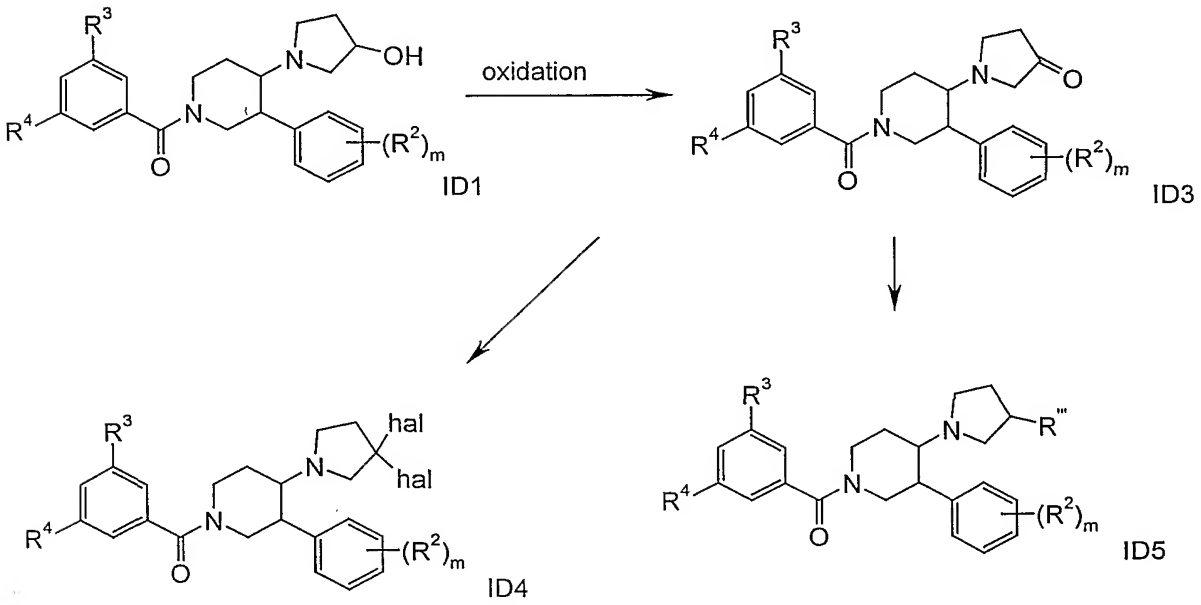



R'''' is morpholinyl, $-NR_2$, -NR-cycloalkyl, -NR-C(O)-cycloalkyl, -NR-C(O)-phenyl or $-NR-C(O)-(CH_2)_n$-phenyl, R, $R^2$, $R^3$, $R^4$ and m have the significances given above and hal is preferably fluoro.

Ketone derivatives of formula IE3 can be obtained by Swern oxidation of an alcohol of formula IE1 by methods known in the art.
Compounds of formula IE4 can be obtained by treating a ketone of formula IE3 with, for example, diethylamino sulfurtrifluoride, in an inert solvent like methylene chloride.

Compounds of formula IE5 can be obtained by reductive amination by treating a ketone of formula IE3 with, for example, titanium(IV) isopropoxide and a mixture of ammonium chloride and triethylamine or a primary or secondary amine and consecutively with sodium borohydride or sodium cyanoborohydride or by substitution of an alcohol IE1 with the sequence (a) reaction with methanesulfonyl chloride and triethylamine in dichloromethane, (b) treatment with sodium azide in dimethylformamide (c), reduction of the intermediate azide with hydrogen and a palladium catalyst (d) alkylation or acylation of the free amine.

Scheme 8




The preparation of compounds shown in scheme 8 is carried out in accordance with the preparation of compounds shown in scheme 7.

R''' is $NR^2$, -N(cycloalkyl)$_2$, -N[$(CH_2)_n$-cycloalkyl]$_2$ or –NR-C(O)-cycloalkyl, R, $R^2$, $R^3$, $R^4$ and m have the significances given above and hal is preferably fluoro.

The salt formation is effected at room temperature in accordance with methods which are known per se and which are familiar to any person skilled in the art. Not only salts with inorganic acids, but also salts with organic acids come into consideration. Hydrochlorides, hydrobromides, sulphates, nitrates, citrates, acetates, maleates, succinates, methane-sulphonates, p-toluenesulphonates and the like are examples of such salts.

As mentioned earlier, the compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacological properties. It has been found that the compounds of the present invention are antagonists of the Neurokinin 1 (NK-1, substance P) receptor.

The compounds were investigated in accordance with the tests given hereinafter.

The affinity of test compounds for the $NK_1$ receptor was evaluated at human $NK_1$ receptors in CHO cells infected with the human $NK_1$ receptor (using the Semliki virus expression system) and radiolabelled with [$^3$H]substance P (final concentration 0.6 nM). Binding assays were performed in HEPES buffer (50 mM, pH 7.4) containing BSA (0.04 %) leupeptin (8 μg / ml), $MnCl_2$ (3 mM) and phosphoramidon (2 μM). Binding assays consisted of 250 μl of membrane suspension ($1.25x10^5$ cells / assay tube), 0.125 μl of buffer of displacing agent and 125 μl of [$^3$H]substance P. Displacement curves were determined with at least seven concentrations of the compound. The assay tubes were incubated for 60 min at room temperature after which time the tube contents were rapidly filtered under vacuum through GF/C filters presoaked for 60 min with PEI (0.3%) with 2 x 2 ml washes of HEPES buffer (50 mM, pH 7.4). The radioactivity retained on the filters was measured by scintillation counting. All assays were performed in triplicate in at least 2 separate experiments.

The affinity to the NK-1 receptor, given as pKi, is in the scope of 6.70 – 9.44 for the compounds of formula I of the present invention. The preferred compounds with a pKi >8.5 are shown in the table below:

| Example No. | pKi | Example No. | pKi |
|---|---|---|---|
| 27 | 8.51 | 103 | 8.67 |
| 36 | 8.90 | 104 | 8.63 |
| 63 | 8.67 | 106 | 8.50 |
| 65 | 8.85 | 107 | 9.20 |
| 66 | 8.56 | 108 | 8.89 |
| 70 | 8.59 | 109 | 8.79 |

| | | | |
|---|---|---|---|
| 77 | 8.53 | 110 | 8.98 |
| 79 | 8.69 | 111 | 9.34 |
| 80 | 8.50 | 112 | 9.10 |
| 82 | 8.68 | 113 | 9.44 |
| 88 | 8.50 | 114 | 9.44 |
| 90 | 8.61 | 115 | 9.04 |
| 92 | 8.57 | 118 | 8.75 |
| 102 | 9.28 | 119 | 9.00 |

Furthermore, it has been shown that the compounds of formula I have a good water-solubility as shown in the table below. This advantage of compounds of formula I over other NK-1-related compounds extends the practicability in administration with regard to certain forms of application.

| | Solubility at pH 6.5 [mg/mL] | Solubility at pH 4.3 [mg/mL] |
|---|---|---|
| Example 27 | 0.91 | >8.4 |
| Example 34 | | >3.5 |
| Example 36 | | >7.5 |
| Example 45 | 1.0 | 2.4 |
| Example 63 | 0.78 | 1.0 |
| Example 102 | 0.43 | 5.5 |

The compounds of formula I as well as their pharmaceutically usable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of general formula I should be appropriate, although the above upper limit can also be exceeded when necessary.

The following Examples illustrate the present invention without limiting it. All temperatures are given in degrees Celsius.

## Example 1

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(3,4-dichloro-phenyl)-3-phenyl-piperidin-1-yl]-methanone

To a suspension of rac-cis-4-(3,4-dichlorophenyl)-3-phenyl-piperidine hydrochloride (200 mg, 0.58 mmol) in 20 mL dichloromethane was added triethylamine (0.35 mL, 2.5 mmol) and 3,5-bistrifluoromethyl-benzoyl chloride (0.11 mL, 0.60 mmol). The reaction mixture was stirred at room temperature overnight and than diluted with 20 mL water. The organic

phase was separated and the aqueous layer was extracted twice with 20 mL dichloromethane. Organic phases were pooled, dried with magnesium sulfate and evaporated. Recrystallization of the crude product from diisopropylether and hexanes gave the desired product (268 mg, 84%) as white crystalls, MS: m/e = 546.1 ($M^+$).

Example 2

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(3,4-diphenyl-piperidin-1-yl)-methanone

The title compound, MS: m/e = 478.2 ($M+H^+$), was prepared in accordance with the general method of example 1 from 3,5-bis(trifluoromethyl)benzoyl chloride and rac-cis-3,4-diphenylpiperidine.

Example 3

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(2-chloro-phenyl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 512.2 ($M^+$), was prepared in accordance with the general method of example 1 from 3,5-bis(trifluoromethyl)benzoyl chloride and rac-cis-4-(o-chlorophenyl)-3-phenylpyridine hydrochloride.

Example 4

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-phenyl-4-(3-trifluoromethyl-phenyl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 546.1 ($M+H^+$), was prepared in accordance with the general method of example 1 from 3,5-bis(trifluoromethyl)benzoyl chloride and rac-cis-3-phenyl-4-(3-trifluoromethylphenyl)piperidine hydrochloride.

Example 5

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(2-chloro-phenyl)-4-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 512.2 ($M^+$), was prepared in accordance with the general method of example 1 from 3,5-bis(trifluoromethyl)benzoyl chloride and rac-cis-3-(2-chloro-phenyl)-4-phenyl-piperidine hydrochloride.

Example 6

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(3-chloro-phenyl)-4-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 512.2 ($M^+$), was prepared in accordance with the general method of example 1 from 3,5-bis(trifluoromethyl)benzoyl chloride and rac-cis-3-(3-chloro-phenyl)-4-phenyl-piperidine hydrochloride.

Example 7

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(3-bromo-phenyl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 556.0 ($M^+$), was prepared in accordance with the general method of example 1 from 3,5-bis(trifluoromethyl)benzoyl chloride and rac-cis-4-(3-bromo-phenyl)-3-phenyl-piperidine hydrochloride.

Example 8

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-chloro-phenyl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 512.2 ($M^+$), was prepared in accordance with the general method of example 1 from 3,5-bis(trifluoromethyl)benzoyl chloride and rac-cis-4-(4-chloro-phenyl)-3-phenyl-piperidine hydrochloride.

Example 9

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 512.2 ($M^+$), was prepared in accordance with the general method of example 1 from 3,5-bis(trifluoromethyl)benzoyl chloride and rac-cis-3-(4-chloro-phenyl)-4-phenyl-piperidine hydrochloride.

Example 10

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-{4-[3-(4-methyl-piperazin-1-yl)-phenyl]-3-phenyl-piperidin-1-yl}-methanone

To a solution of rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(3-bromo-phenyl)-3-phenyl-piperidin-1-yl]-methanone (500 mg, 0.899 mmol) in 5 mL dry toluene was added 1-

methyl-piperazine (0.123 mL, 1.08 mmol), sodium tert.-butoxide (125 mg, 1.26 mmol), bis(dibenzylidenacetone)palladium (2.1 mg, 0.002 mmol) and rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (4.3 mg, 0.007 mmol) and than refluxed overnight. The reaction mixture was diluted with 10 mL water and extracted three times with 20 mL ethyl acetate. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with hexane/ethyl acetate/triethyl amine 10:10:1 gave the desired product (196 mg, 38%), MS: m/e = 576.1 ($M+H^+$).

Example 11

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(3-morpholin-4-yl-phenyl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 563.3 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(3-bromo-phenyl)-3-phenyl-piperidin-1-yl]-methanone and morpholine.

Example 12

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-phenyl-4-(3-phenylamino-phenyl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 569.2 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(3-bromo-phenyl)-3-phenyl-piperidin-1-yl]-methanone and aniline.

Example 13

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-phenyl-4-(3-pyrrolidin-1-yl-phenyl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 547.2 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(3-bromo-phenyl)-3-phenyl-piperidin-1-yl]-methanone and pyrrolidine.

Example 14

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-{4-[3-(2-methoxy-ethylamino)-phenyl]-3-phenyl-piperidin-1-yl}-methanone

The title compound, MS: m/e = 551.1 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(3-bromo-phenyl)-3-phenyl-piperidin-1-yl]-methanone and 2-methoxy ethylamine.

Example 15

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(3-diethylamino-phenyl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 549.2 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(3-bromo-phenyl)-3-phenyl-piperidin-1-yl]-methanone and diethylamine.

Example 16

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-{4-[3-(cyclopropylmethyl-amino)-phenyl]-3-phenyl-piperidin-1-yl}-methanone

The title compound, MS: m/e = 547.2 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(3-bromo-phenyl)-3-phenyl-piperidin-1-yl]-methanone and aminomethylcyclopropane.

Example 17

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-morpholin-4-yl-phenyl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 563.3 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-chloro-phenyl)-3-phenyl-piperidin-1-yl]-methanone, morpholine and biphenyl-2-yl-dicyclohexyl-phosphane as ligand.

Example 18

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-{4-[4-(4-methyl-piperazin-1-yl)-phenyl]-3-phenyl-piperidin-1-yl}-methanone

The title compound, MS: m/e = 576.1 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-chloro-phenyl)-3-phenyl-piperidin-1-yl]-methanone, N-methyl-piperazine and biphenyl-2-yl-dicyclohexyl-phosphane as ligand.

Example 19

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-phenyl-4-(4-pyrrolidin-1-yl-phenyl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 547.2 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-chloro-phenyl)-3-phenyl-piperidin-1-yl]-methanone, pyrrolidine and biphenyl-2-yl-dicyclohexyl-phosphane as ligand.

Example 20

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-{4-[4-(2-methoxy-ethylamino)-phenyl]-3-phenyl-piperidin-1-yl}-methanone

The title compound, MS: m/e = 551.1 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-chloro-phenyl)-3-phenyl-piperidin-1-yl]-methanone, 2-methoxy-ethylamine and biphenyl-2-yl-dicyclohexyl-phosphane as ligand.

Example 21

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-{3-[3-(3-methoxy-propylamino)-phenyl]-4-phenyl-piperidin-1-yl}-methanone

The title compound, MS: m/e = 565.4 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(3-chloro-phenyl)-4-phenyl-piperidin-1-yl]-methanone, 3-methoxy-propylamine and biphenyl-2-yl-dicyclohexyl-phosphane as ligand.

Example 22

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-phenyl-3-(3-pyrrolidin-1-yl-phenyl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 547.4 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(3-chloro-phenyl)-4-phenyl-piperidin-1-yl]-methanone, pyrrolidine and biphenyl-2-yl-dicyclohexyl-phosphane as ligand.

Example 23

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-{4-[2-(2-methoxy-ethylamino)-phenyl]-3-phenyl-piperidin-1-yl}-methanone

The title compound, MS: m/e = 551.1 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(2-chloro-

phenyl)-3-phenyl-piperidin-1-yl]-methanone, 2-methoxy-ethylamine and biphenyl-2-yl-dicyclohexyl-phosphane as ligand.

Example 24

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-{4-[2-(2-dimethylamino-ethylamino)-phenyl]-3-phenyl-piperidin-1-yl}-methanone

The title compound, MS: m/e = 564.3 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(2-chloro-phenyl)-3-phenyl-piperidin-1-yl]-methanone, N,N-dimethyl-ethylendiamine and biphenyl-2-yl-dicyclohexyl-phosphane as ligand.

Example 25

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-morpholin-4-yl-phenyl)-4-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 563.3 ($M^+$), was prepared in accordance with the general method of example 10 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-phenyl-piperidin-1-yl]-methanone, morpholine and biphenyl-2-yl-dicyclohexyl-phosphane as ligand.

Example 26

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(4-morpholin-4-yl-3-phenyl-piperidin-1-yl)-methanone

To a mixture of 1-benzyl-3-phenyl-piperidin-4-one (2.07 g, 7.78 mmol) and morpholine (678 mg, 7.78 mmol) was added tetraisopropyl-orthotitanate (2.97 mL, 9.73 mmol) at room temperature. After stirring at room temperature overnight the reaction mixture was diluted with ethanol (8.0 mL) and sodium cyanoborohydride (369 mg, 5.37 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and was diluted with water (2.0 mL). The anorganic precipitate was filtered off and washed with ethanol. The filtrate was evaporated and purified by flash chromatography on silica gel with toluene/ethyl acetate 6:1 to give rac-cis-4-(1-benzyl-3-phenyl-piperidin-4-yl)-morpholine (1.42 g, 54%) as a yellow solid, MS: m/e = 337.3 ($M+H^+$).

Rac-cis-4-(1-benzyl-3-phenyl-piperidin-4-yl)-morpholine (1.3 g, 3.86 mmol) was dissolved in methanol (50 mL) and concentrated hydrochloric acid (0.2 mL) and palladium on charcoal (10%, 200 mg) were added. After stirring in a hydrogen atmosphere (1 bar) at room temperature overnight the mixture was filtered and the solvent was

evaporated. The crude intermediate was dissolved in dichloromethane (20 mL) and triethylamine (2.69 mL, 19.3 mmol) and 3,5-bistrifluoromethyl-benzoyl chloride (0.91 mL, 5.02 mmol) were added. The reaction mixture was stirred at room temperature overnight and than diluted with 20 mL water. The organic phase was separated and the aqueous layer was extracted twice with 20 mL dichloromethane. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with hexane/ethyl acetate/triethyl amine 80:20:1 gave the desired product (1.57 g, 83%) as off-white crystalls, MS: m/e = 487.3 ($M+H^+$).

Example 27

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-methyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 500.2 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-phenyl-piperidin-4-one, N-methyl-piperazine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 28

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(4-morpholin-4-yl-3-o-tolyl-piperidin-1-yl)-methanone

The title compound, MS: m/e = 501.2 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-o-tolyl-piperidin-4-one, morpholine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 29

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-methyl-piperazin-1-yl)-3-o-tolyl-piperidin-1-yl]-methanone

The title compound, MS: m/e =.514.3 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-o-tolyl-piperidin-4-one, N-methyl-piperazine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 30

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(2-chloro-phenyl)-4-morpholin-4-yl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 521.1 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-(2-chloro-phenyl)-piperidin-4-one, morpholine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 31

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(2-chloro-phenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 534.2 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-(2-chloro-phenyl)-piperidin-4-one, N-methyl-piperazine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 32

Rac-cis-1-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone

To a mixture of 1-benzyl-3-phenyl-piperidin-4-one (10.0 g, 37.7 mmol) and piperazine (13.0 g, 151 mmol) was added tetraisopropyl-orthotitanate (42.8 mL, 151 mmol) at room temperature. After stirring at room temperature overnight the reaction mixture was diluted with ethanol (300 mL) and sodium cyanoborohydride (10.5 g, 151 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and was diluted with water (10 mL). The anorganic precipitate was filtered off and washed with ethanol. The solvent was evaporated and the residue was taken up in ethylenglycol (130 mL) and sodium hydroxide (13.6 g, 37.7 mmol) was added. The reaction mixture was stirred at 130°C for 15 min. After cooling water (200 mL) was added and the mixture was extracted twice with 200 mL diethylether. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with methylene chloride/triethyl amine 99:1 gave rac-cis-1-(1-benzyl-3-phenyl-piperidin-4-yl)-piperazine (4.63 g, 36%) as a yellow oil, MS: m/e = 336.3 ($M+H^+$).

Rac-cis-1-(1-benzyl-3-phenyl-piperidin-4-yl)-piperazine (4.62 g, 13.8 mmol) was dissolved in methylene chloride (100 mL) and 4-dimethylaminopyridine (29 mg, 0.14 mmol) was added. The reaction mixture was cooled with an ice bath and pyridine (2.78 mL, 34.4 mmol) and trifluoroacetic acid anhydride (2.68 mL, 19.3 mmol) were added sequentially. The mixture was stirred at room temperature overnight and water (100 mL) was added. The organic phase was separated and the aqueous layer was extracted twice with 100 mL methylene chloride. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with hexane/ethyl acetate/triethyl amine

90:10:1 gave rac-cis-1-[4-(1-benzyl-3-phenyl-piperidin-4-yl)-piperazin-1-yl]-2,2,2-trifluoro-ethanone (4.64 g, 78%) as a light yellow oil, MS: m/e = 432.5 ($M+H^+$).

Rac-cis-1-[4-(1-benzyl-3-phenyl-piperidin-4-yl)-piperazin-1-yl]-2,2,2-trifluoro-ethanone (4.60 g, 10.7 mmol) was dissolved in methanol (200 mL) and concentrated hydrochloric acid (1.0 mL) and palladium on charcoal (10%, 700 mg) were added. After stirring in a hydrogen atmosphere (1 bar) at room temperature overnight the mixture was filtered and the solvent was evaporated. The crude intermediate was dissolved in dichloromethane (100 mL) and triethylamine (7.25 mL, 51.7 mmol) and 3,5-bistrifluoromethyl-benzoyl chloride (2.06 mL, 11.4 mmol) were added. The reaction mixture was stirred at room temperature overnight and than diluted with 100 mL water. The organic phase was separated and the aqueous layer was extracted twice with 100 mL dichloromethane. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with hexane/ethyl acetate/triethyl amine 90:10:1 gave the desired product (5.26 g, 87%) as a white foam, MS: m/e = 582.0 ($M+H^+$).

Example 33

Rac-cis-{4-[4-(3,5-Bis-trifluoromethyl-benzoyl)-piperazin-1-yl]-3-phenyl-piperidin-1-yl}-(3,5-bis-trifluoromethyl-phenyl)-methanone

The title compound, MS: m/e = 726.1 ($M+H^+$), was obtained as a by-product of rac-cis-1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone (example 32).

Example 34

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone

Rac-cis-1-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone (4.15 g, 7.14 mmol) was dissolved in methanol (25 mL). Water (1 mL) and potassium carbonate (2.96 g, 21.4 mmol) were added and the reaction mixture was stirred at room temperature for 4 h. Water (100 mL) was added and the mixture was extracted twice with 200 mL methylene chloride. Organic phases were pooled and dried with magnesium sulfate. Evaporation of the solvent gave the title compound (3.4 g, 98%) as a white foam which was used without any further purification, MS: m/e = 486.3 ($M+H^+$).

Example 35

Rac-cis-2 {4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-N,N-dimethyl-acetamide

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone (200 mg, 0.41 mmol) was dissolved in N,N-dimethylforamide (5 mL). Potassium carbonate (171 mg, 1.24 mmol) and 2-chloro-N,N-dimethylacetamide (0.042 mL, 0.41 mmol) were added and the reaction mixture was stirred at room temperature overnight. Water (50 mL) was added and the mixture was extracted twice with 100 mL ethyl acetate. Organic phases were pooled, dried with magnesium sulfate and evaporated. Chromatography on silica gel with methylen chloride/methanol/triethyl amine 90:10:1 gave the desired product (200 mg, 85%) as an off-white solid, MS: m/e = 571.1 ($M+H^+$).

Example 36

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropylmethyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 540.3 ($M+H^+$), was prepared in accordance with the general method of example 35 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and bromomethyl cyclopropane.

Example 37

Rac-cis-[4-(4-Benzyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone

The title compound, MS: m/e = 576.1 ($M+H^+$), was prepared in accordance with the general method of example 35 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and benzyl bromide.

Example 38

Rac-cis-1-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-ethanone

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone (200 mg, 0.41 mmol) was dissolved in methylene chloride (5 mL). Triethyl amine (0.173 mL, 1.24 mmol) and acetyl chloride (0.035 mL, 0.49 mmol) were added and the reaction mixture was stirred at room temperature overnight. The solvent was

evaporated and chromatography on silica gel with methylen chloride/triethyl amine 99:1 gave the desired product (122 mg, 56%) as a light yellow foam, MS: m/e = 528.2 ($M+H^+$).

Example 39

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 554.2 ($M+H^+$), was prepared in accordance with the general method of example 38 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and cyclopropane carboxylic acid chloride.

Example 40

Rac-cis-[4-(4-Benzoyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone

The title compound, MS: m/e = 590.2 ($M+H^+$), was prepared in accordance with the general method of example 38 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and benzoyl chloride.

Example 41

Rac-cis-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-morpholin-4-yl-methanone

The title compound, MS: m/e = 599.1 ($M+H^+$), was prepared in accordance with the general method of example 38 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and 4-morpholine carbonyl chloride.

Example 42

Rac-cis-4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazine-1-carboxylic acid 2-dimethylamino-ethyl ester

The title compound, MS: m/e = 601.1 ($M+H^+$), was prepared in accordance with the general method of example 35 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and N-(2-chloroethyl)-N,N-dimethylamine.

Example 43

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 526.1 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-phenyl-piperidin-4-one, N-cyclopropyl-piperazine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 44

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(4-hydroxy-3'-phenyl-[1,4']bipiperidinyl-1'-yl)-methanone

The title compound, MS: m/e = 501.2 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-phenyl-piperidin-4-one, 4-hydroxy-piperidine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 45

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 518.2 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-(4-fluoro-phenyl)-piperidin-4-one, N-methyl-piperazine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 46

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-morpholin-4-yl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 505.3 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-(4-fluoro-phenyl)-piperidin-4-one, morpholine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 47

Rac-cis-2-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-N-(2,6-dimethyl-phenyl)-acetamide

The title compound, MS: m/e = 647.2 ($M+H^+$), was prepared in accordance with the general method of example 35 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and N-chloroacetyl-2,6-dimethylaniline.

Example 48

(3R,3'R,4S)- and (3S,3'R,4R)-(3,5-Bis-trifluoromethyl-phenyl)-[4-(3'-hydroxy-pyrrolidin-1'-yl)-3-phenyl-piperidin-1-yl]-methanone

A mixture of the title compounds, MS: m/e = 487.3 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-phenyl-piperidin-4-one, (R)-3-hydroxypyrrolidine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 49

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(3-phenyl-4-thiomorpholin-4-yl-piperidin-1-yl)-methanone

The title compound, MS: m/e = 503.2 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-phenyl-piperidin-4-one, thiomorpholine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 50

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(1-oxo-1l 4-thiomorpholin-4-yl)-3-phenyl-piperidin-1-yl]-methanone

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(3-phenyl-4-thiomorpholin-4-yl-piperidin-1-yl)-methanone (190 mg, 0.38 mmol) was dissolved in methanol (5 mL). Potassium peroxymonosulfat (Oxone) (140 mg, 0.23 mmol) was added and the reaction mixture was stirred at room temperature for 3 days. The salts were filtered off and the filtrate was evaporated. Chromatography on silica gel with methylen chloride/methanol/triethyl amine 98:1:1 gave the desired product (163 mg, 83%) as an off-white solid, MS: m/e = 519.2 ($M+H^+$).

Example 51

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(1,1-dioxo-1l 6-thiomorpholin-4-yl)-3-phenyl-piperidin-1-yl]-methanone

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(3-phenyl-4-thiomorpholin-4-yl-piperidin-1-yl)-methanone (200 mg, 0.40 mmol) was dissolved in methanol (5 mL). Potassium peroxymonosulfate (Oxone) (540 mg, 0.88 mmol) was added and the reaction mixture was stirred at room temperature for 3 days. Sodium hydrogen sulfite solution (40%, 5 mL) was added and the mixture was stirred at room temperature for 30 min. Sodium bicarbonate solution (2N, 20 mL) was added and the mixture was extracted three times with methylen

chloride (30 mL). Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with hexane/ethyl acetate/triethyl amine 10:90:1 gave the desired product (204 mg, 96%) as a white foam, MS: m/e = 535.2 ($M+H^+$).

Example 52

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-morpholin-4-yl-piperidin-1-yl]-methanone

To a mixture of 1-benzyl-3-(4-chloro-phenyl)-piperidin-4-one (1.0 g, 3.34 mmol) and morpholine (1.16 mL, 13.3 mmol) was added tetraisopropyl-orthotitanate (3.95 mL, 13.3 mmol) at room temperature. After stirring at room temperature overnight the reaction mixture was diluted with ethanol (30.0 mL) and sodium cyanoborohydride (930 mg, 13.3 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and was diluted with water (2.0 mL). The anorganic precipitate was filtered off and washed with ethanol. The filtrate was evaporated and purified by flash chromatography on silica gel with hexane/ethyl acetate/triethylamine 40:10:1 to give rac-cis-4-[1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-morpholine (650 mg, 52%) as a yellow solid, MS: m/e = 371.3 ($M+H^+$).

Rac-cis--4-[1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-morpholine (650 mg, 1.75 mmol) was dissolved in dichloromethane (15 mL) and 1-chloroethyl-chloroformate (0.575 mL, 5.27 mmol) were added at 0°C. The reaction mixture was refluxed overnight. Methanol (15 mL) was added and reflux was continued for 3h. The solvents were evaporated. The crude intermediate was dissolved in dichloromethane (30 mL) and triethylamine (1.22 mL, 8.75 mmol) and 3,5-bistrifluoromethyl-benzoyl chloride (0.35 mL, 1.93 mmol) were added. The reaction mixture was stirred at room temperature overnight and than diluted with 50 mL water. The organic phase was separated and the aqueous layer was extracted twice with 50 mL dichloromethane. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with hexane/ethyl acetate/triethylamine 20:10.1 gave the desired product (820 mg, 90%) as a yellow solid, MS: m/e = 521.1 ($M+H^+$).

Example 53

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(4-cyclopropylmethoxy-3'-phenyl-[1,4']bipiperidinyl-1'-yl)-methanone

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(4-hydroxy-3'-phenyl-[1,4']bipiperidinyl-1'-yl)-methanone (100 mg, 0.20 mmol) was dissolved in dimethylformamide (2 mL). Sodium

hydride (17 mg, 55%, 0.40 mmol) and bromomethyl cyclopropane (0.038 mL, 0.40 mmol) were added and the reaction mixture was stirred at room temperature overnight. Water (5 mL) was added and the mixture was extracted three times with ethyl acetate (20 mL). Organic phases were pooled, dried with magnesium sulfate and evaporated. Chromatography on silica gel with methylene chloride/methanol/ triethyl amine 98:1:1 gave the desired product (95 mg, 85%) as an off-white solid, MS: m/e = 555.1 ($M+H^+$).

Example 54

(3R,3'R,4S)- and (3S,3'R,4R)-(3,5-Bis-trifluoromethyl-phenyl)-[4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-3-phenyl-piperidin-1-yl]-methanone

A mixture of the title compounds, MS: m/e = 541.2 ($M+H^+$), was prepared in accordance with the general method of example 53 from (3R,3'R,4R)- and (3S,3'R,4S)-(3,5-bis-trifluoromethyl-phenyl)-[4-(3'-hydroxy-pyrrolidin-1'-yl)-3-phenyl-piperidin-1-yl]-methanone and bromomethyl cyclopropane.

Example 55

Rac-cis-1'-(3,5-Bis-trifluoromethyl-benzoyl)-3'-phenyl-[1,4']bipiperidinyl-4-one

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(4-hydroxy-3'-phenyl-[1,4']bipiperidinyl-1'-yl)-methanone (1.02 g, 2.04 mmol) was dissolved in methylene chloride (10 mL). Oxalyl chloride (0.21 mL, 2.45 mmol) and dimethylsulfoxide (0.29mL, 4.07 mmol) were added at -78°C and the reaction mixture was stirred at -78°C for 3h. Triethyl amine (1.14 mL, 8.15 mmol) was added and the reaction mixture was slowly warmed to room temperature. Stirring was continued at room temperature overnight. Water (10 mL) was added and the mixture was extracted three times with methylene chloride (20 mL). Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with hexane/ethyl acetate/triethyl amine 70:30:1 gave the desired product (584 mg, 57%) as a white foam, MS: m/e = 499.2 ($M+H^+$).

Example 56

Rac-cis-1-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-pyrrolidin-3-one

The title compound, MS: m/e = 485.3 ($M+H^+$), was prepared in accordance with the general method of example 55 from (3R,3'R,4R)- and (3S,3'R,4S)-(3,5-bis-trifluoromethyl-phenyl)-[4-(3'-hydroxy-pyrrolidin-1'-yl)-3-phenyl-piperidin-1-yl]-methanone.

Example 57

Rac-cis- (3,5-Bis-trifluoromethyl-phenyl)-(4,4-difluoro-3'-phenyl-[1,4']bipiperidinyl-1'-yl)-methanone

Rac-cis-1'-(3,5-Bis-trifluoromethyl-benzoyl)-3'-phenyl-[1,4']bipiperidinyl-4-one (183 mg, 0.367 mmol) was dissolved in methylene chloride (5 mL). Diethylamino sulfurtrifluoride (0.062 mL, 0.50 mmol) was added at -78°. The reaction mixture was stirred at -78°C for 3h then slowly warmed to room temperature and stirring was continued at room temperature overnight. The solvent was evaporated and chromatography on silica gel with hexane/ethyl acetate/triethyl amine 10:10:1 gave the desired product (83 mg, 43%) as an off-white solid, MS: m/e = 521.2 ($M+H^+$).

Example 58

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-(3,5-Bis-trifluoromethyl-phenyl)-[3'-(4-fluoro-phenyl)-3-hydroxy-[1,4']bipiperidinyl-1'-yl]-methanone

The title compound, MS: m/e = 519.2 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-(4-fluoro-phenyl)-piperidin-4-one, (rac)-3-hydroxy-piperidine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 59

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-phenyl-4-(4-pyrimidin-2-yl-piperazin-1-yl)-piperidin-1-yl]-methanone

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone (300 mg, 0.62 mmol) and 2-chloropyrimidine (71 mg, 0.68) were stirred at 100°C overnight. The reaction mixture was taken up in 1 mL methylene chloride and chromatographed on silica gel with methylen chloride/methanol/triethyl amine 90:10:1. The desired product (181 mg, 47%) was a light yellow solid, MS: m/e = 564.3 ($M+H^+$).

Example 60

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-phenyl-4-(2,3,5,6-tetrahydro-[1,2']bipyrazinyl-4-yl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 564.3 ($M+H^+$), was prepared in accordance with the general method of example 59 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and 2-chloropyrazine.

Example 61

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(3,3-difluoro-pyrrolidin-1-yl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 507.5 ($M+H^+$), was prepared in accordance with the general method of example 57 from rac-cis-1-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-pyrrolidin-3-one.

Example 62

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-pyrrolidin-1-yl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 489.3 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-(4-fluoro-phenyl)-piperidin-4-one, pyrrolidine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 63

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-hydroxy-[1,4']bipiperidinyl-1'-yl]-methanone

To a mixture of 1-benzyl-3-(4-chloro-phenyl)-piperidin-4-one (3.32 g, 11.1 mmol) and 4-hydroxy-piperidine (1.23 g, 12.2 mmol) was added tetraisopropyl-orthotitanate (3.94 g, 13.8 mmol) at room temperature. After stirring at room temperature overnight the reaction mixture was diluted with ethanol (30.0 mL) and sodium cyanoborohydride (905 mg, 14.4 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and was diluted with water (2.0 mL). The anorganic precipitate was filtered off and washed with ethanol. The filtrate was evaporated and purified by flash chromatography on silica gel with dichloromethane/methanol/ammonia 100:4:0.4 to give rac-cis-1'-benzyl-3'-(4-chloro-phenyl)-[1,4']bipiperidinyl-4-ol (2.25 g, 53%) as a white foam, MS: m/e = 385.3 ($M+H^+$).

Rac-cis-1'-benzyl-3'-(4-chloro-phenyl)-[1,4']bipiperidinyl-4-ol (2.17 g, 5.64 mmol) was dissolved in dimethylformamide (8 mL) and imidazole (1.15 g, 16.9 mmol) and tert.butyl-dimethyl-silylchloride (1.70 g, 11.3 mmol) were added. The reaction mixture was stirred at 40°C overnight and than diluted with 50 mL water. The mixture was extracted three times with 50 mL ethyl acetate. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with hexane/ethyl acetate/triethyl amine 80:10:1 gave rac-cis-1'-benzyl-4-(tert-butyl-dimethyl-silanyloxy)-3'-(4-chloro-phenyl)-[1,4']bipiperidinyl (2.80 g, 99%) as a colorless oil, MS: m/e = 499.3 ($M^+$).

Rac-cis-1'-benzyl-4-(tert-butyl-dimethyl-silanyloxy)-3'-(4-chloro-phenyl)-[1,4']bipiperidinyl (2.80 g, 5.60 mmol) were dissolved in dichloromethane (45 mL) and 1-chloroethyl-chloroformate (1.83 mL, 16.8 mmol) were added at 0°C. The reaction mixture was refluxed overnight. Methanol (40 mL) was added and reflux was continued for 3h. The solvents were evaporated. The crude intermediate was dissolved in dichloromethane (100 mL) and triethylamine (3.9 mL, 28 mmol) and 3,5-bistrifluoromethyl-benzoyl chloride (1.11mL, 6.16 mmol) were added. The reaction mixture was stirred at room temperature overnight and than diluted with 50 mL water. The organic phase was separated and the aqueous layer was extracted twice with 50 mL dichloromethane. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with dichloromethane/methanol/ammonia 140:10:1 gave the desired product (1.57 g, 83%) as a white foam, MS: m/e = 535.2 ($M+H^+$).

Example 64

Rac-cis-4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazine-1-carboxylic acid diethylamide

The title compound, MS: m/e = 584.2 ($M+H^+$), was prepared in accordance with the general method of example 38 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and diethyl carbonyl chloride.

Example 65

(+)-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone was separated on chiralpac AD with 10% ethanol in heptane. The second fraction contained the more active enantiomer, $[\alpha]_{589}^{20} = +18.18$ (c = 0.9679, methanol).

Example 66

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-cyclopropylmethoxy-[1,4']bipiperidinyl-1'-yl]-methanone

The title compound, MS: m/e = 589.2 ($M+H^+$), was prepared in accordance with the general method of example 53 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-hydroxy-[1,4']bipiperidinyl-1'-yl]-methanone and bromomethyl cyclopropane.

Example 67

Rac-cis-1'-(3,5-Bis-trifluoromethyl-benzoyl)-3'-(4-chloro-phenyl)-[1,4']bipiperidinyl-4-one

The title compound, MS: m/e = 533.2 ($M+H^+$), was prepared in accordance with the general method of example 55 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-hydroxy-[1,4']bipiperidinyl-1'-yl]-methanone.

Example 68

Rac-cis-2-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-N-(4-fluoro-phenyl)-acetamide

The title compound, MS: m/e = 637.1 ($M+H^+$), was prepared in accordance with the general method of example 35 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and α-chloro-4-fluoroacetamide.

Example 69

Rac-cis-2-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-1-morpholin-4-yl-ethanone

The title compound, MS: m/e = 613.1 ($M+H^+$), was prepared in accordance with the general method of example 35 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and 4-(2-chloroacetyl)morpholine.

Example 70

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-morpholin-4-yl-piperidin-1-yl]-methanone

Rac-cis)-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-morpholin-4-yl-piperidin-1-yl]-methanone was separated on chiralpac AD with 15% ethanol in heptane. The second fraction contained the more active enantiomer, $[\alpha]_{589}^{20} = -48.61$ (c = 0.5678, methanol).

Example 71

Rac-cis-1-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone

The title compound, MS: m/e = 604.1 ($M+H^+$), was prepared in accordance with the general method of example 38 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and phenylacetylchloride.

Example 72

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-pyrrolidin-1-yl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 505.2 ($M+H^+$), was prepared in accordance with the general method of example 52 from 1-benzyl-3-(4-chloro-phenyl)-piperidin-4-one, pyrrolidine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 73

(3R,3'R,4S)- and (3S,3'R,4R)-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-(3-hydroxy-pyrrolidin-1-yl)-piperidin-1-yl]-methanone

A mixture of the title compounds, MS: m/e = 505.2 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-(4-fluoro-phenyl)-piperidin-4-one, (R)-3-hydroxypyrrolidine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 74

Rac-cis-[4-(4-Benzooxazol-2-yl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone

The title compound, MS: m/e = 603.0 ($M+H^+$), was prepared in accordance with the general method of example 59 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and 2-chlorobenzoxazole.

Example 75

(1'R,3R,4R)- and (1'R,3S,4S)4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazine-1-carboxylic acid (1-phenyl-ethyl)-amide

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone (204 mg, 0.42 mmol) was dissolved in methylene chloride (5 mL). (R)-alpha-Methylbenzyl-isocyanate (0.066 mL, 0.46 mmol) was added and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the product (256 mg, 96%) was obtained as an off-white foam, MS: m/e = 633.1 ($M+H^+$).

Example 76

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-Cyclopropanecarboxylic acid {1-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-pyrrolidin-3-yl}-methyl-amide

Rac-cis-1-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-pyrrolidin-3-one (767 mg, 1.58 mmol) was dissolved in ethanol (15 mL). Methylamine hydrochloride (139 mg, 2.06 mmol), triethylamine (417 mg, 4.12 mmol) and tetraisopropyl-orthotitanate (675 mg, 2.38 mmol) were added. After stirring at room temperature sodium borohydride (102 mg, 2.69 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and was diluted with water (2.0 mL). The anorganic precipitate was filtered off and washed with ethanol. The filtrate was evaporated and purified by flash chromatography on silica gel with methylene chloride/methanol/triethylamine 98:1:1 to give (3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-[4-(3-methyl-amino-pyrrolidin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone (174 mg, 22%) as a brown foam which was not further characterized.

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-[4-(3-methyl-amino-pyrrolidin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone was reacted with cyclopropane carboxylic acid chloride as describe in example 38 to obtain the title compound, MS: m/e = 568.2 ($M+H^+$).

Example 77

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-Cyclopropanecarboxylic acid [1'-(3,5-bis-trifluoromethyl-benzoyl)-3'-(4-fluoro-phenyl)-[1,4']bipiperidinyl-3-yl]-amide

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-(3,5-Bis-trifluoromethyl-phenyl)-[3'-(4-fluoro-phenyl)-3-hydroxy-[1,4']bipiperidinyl-1'-yl]-methanone (1.39 g, 2.68 mmol) was dissolved in dichloromethane (15 mL) and triethylamine (0.934 mL, 6.70 mmol) and methanesulfonyl chloride (0.292 mL, 3.75 mmol) were added at room temperature. The reaction mixture was stirred at room temperature for 30 min and than diluted with 20 mL water. The organic phase was separated and the aqueous layer was extracted twice with 30 mL dichloromethane. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with cyclohexane/ethyl acetate/triethylamine 90:10:1 gave (3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-(3,5-bis-trifluoromethyl-phenyl)-[3-chloro-3'-(4-fluoro-phenyl)-[1,4']bipiperidinyl-1'-yl]-methanone (765 mg, 53%) as a white foam, MS: m/e = 537.2 ($M+H^+$).

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-(3,5-Bis-trifluoromethyl-phenyl)-[3-chloro-3'-(4-fluoro-phenyl)-[1,4']bipiperidinyl-1'-yl]-methanone (696 mg, 1.30 mmol) was dissolved in

N,N-dimethylformamide (15 mL) and sodium azide (505 mg, 7.79 mmol) was added at room temperature. The reaction mixture was stirred at 95°C overnight and than diluted with 50 mL water. The mixture was extracted three times with 50 mL tert.-butyl-methyl ether. Organic phases were pooled, dried with magnesium sulfate and evaporated. The crude azide (704 mg, 100%) was used for the next steps without further purification.

The intermediate azide (704 mg, 1.30 mmol) was dissolved in methanol (50 mL) and palladium on charcoal (10%, 138 mg) was added. After stirring in a hydrogen atmosphere (1 bar) at room temperature overnight the mixture was filtered and the solvent was evaporated. The crude amine (490 mg, 73%) was used for the next step without further purification.

The intermediate amine (163 mg, 0.315 mmol) was dissolved in dichloromethane (5 mL) and triethylamine (0.132 mL, 0.945 mmol) and cyclopropane carboxylic acid chloride (0.035 mL, 0.378 mmol) were added at room temperature. The solvent was evaporated and flash chromatography on silica gel with cyclohexane/ethyl acetate/triethylamine 10:10:1 gave (3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-(cyclopropanecarboxylic acid [1'-(3,5-bis-trifluoromethyl-benzoyl)-3'-(4-fluoro-phenyl)-[1,4']bipiperidinyl-3-yl]-amide (95 mg, 52%) as a light yellow foam, MS: m/e = 586.1 ($M+H^+$).

Example 78

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-N-[1'-(3,5-Bis-trifluoromethyl-benzoyl)-3'-(4-fluoro-phenyl)-[1,4']bipiperidinyl-3-yl]-benzamide

The title compound, MS: m/e = 622.1 ($M+H^+$), was prepared in accordance with the general method of example 77 from the intermediate crude amine and benzoyl chloride.

Example 79

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-N-[1'-(3,5-Bis-trifluoromethyl-benzoyl)-3'-(4-fluoro-phenyl)-[1,4']bipiperidinyl-3-yl]-2-phenyl-acetamide

The title compound, MS: m/e = 636.2 ($M+H^+$), was prepared in accordance with the general method of example 77 from the intermediate crude amine and phenylacetyl chloride.

Example 80

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-pyrrolidin-1-yl-piperidin-1-yl]-methanone

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-pyrrolidin-1-yl-piperidin-1-yl]-methanone was separated on chiralpac AD with 5% ethanol in heptane. The second fraction contained the more active enantiomer, $[\alpha]_{589}^{20}$ = -42.97, $[\alpha]_{546}^{20}$ = -51.90, $[\alpha]_{436}^{20}$ = -100.61, $[\alpha]_{365}^{20}$ = -189.94 (HCl-salt, c = 0.4702, methanol).

Example 81

Rac-cis-1-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4-fluoro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone

The title compound, MS: m/e = 600.0 ($M+H^+$), was prepared in accordance with the general method of example 32 from 1-benzyl-3-(4-fluoro-phenyl)-piperidin-4-one, piperazine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 82

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-piperazin-1-yl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 504.3 ($M+H^+$), was prepared in accordance with the general method of example 34 from rac-cis-1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-fluoro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone.

Example 83

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-{3-(4-fluoro-phenyl)-4-[4-(2,2,2-trifluoro-ethyl)-piperazin-1-yl]-piperidin-1-yl}-methanone

The title compound, MS: m/e = 586.1 ($M+H^+$), was obtained as a by-product of rac-cis-1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-fluoro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone (example 81).

Example 84

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 572.1 ($M+H^+$), was prepared in accordance with the general method of example 38 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-piperazin-1-yl-piperidin-1-yl]-methanone and cyclopropane carboxylic acid chloride.

Example 85

(+)-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-methanone

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-methanone was separated on chiralpac AD with 10% ethanol in heptane. The second fraction contained the more active enantiomer, $[\alpha]_{589}^{20}$ = +14.52 (c = 0.4615, methanol).

Example 86

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-phenyl-4-(4-pyridin-2-yl-piperazin-1-yl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 563.3 ($M+H^+$), was prepared in accordance with the general method of example 59 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and 2-chloropyridine.

Example 87

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(3,4-dichloro-phenyl)-4-morpholin-4-yl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 555.1 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-(3,4-dichloro-phenyl)-piperidin-4-one, morpholine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 88

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropylmethyl-piperazin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 558.3 ($M+H^+$), was prepared in accordance with the general method of example 35 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-piperazin-1-yl-piperidin-1-yl]-methanone and bromomethyl cyclopropane.

Example 89

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-chloro-3-fluoro-phenyl)-4-morpholin-4-yl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 539.3 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-(4-chloro-3-fluoro-phenyl)-piperidin-4-one, morpholine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 90

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone

Rac-cis)-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone was separated on chiralpac AD with 5% isopropanol in heptane. The first fraction contained the more active enantiomer, $[\alpha]_{589}^{20} = -11.70$ (c = 0.3846, chloroform).

Example 91

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-thiomorpholin-4-yl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 537.2 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-(4-chloro-phenyl)-piperidin-4-one, thiomorpholine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 92

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[3-phenyl-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone

Rac-cis)-(3,5-Bis-trifluoromethyl-phenyl)-[3-phenyl-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone was separated on chiralpac AD with 4% isopropanol in heptane. The first fraction contained the more active enantiomer, $[\alpha]_{589}^{20} = -11.55$ (c = 0.3291, chloroform).

Example 93

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4,4-difluoro-[1,4']bipiperidinyl-1'-yl]-methanone

The title compound, MS: m/e = 555.1 ($M+H^+$), was prepared in accordance with the general method of example 57 from rac-cis-1'-(3,5-bis-trifluoromethyl-benzoyl)-3'-(4-chloro-phenyl)-[1,4']bipiperidinyl-4-one and diethylamino sulfurtrifluoride.

Example 94

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-(1,1-dioxo-1l 6-thiomorpholin-4-yl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 569.1 ($M+H^+$), was prepared in accordance with the general method of example 51 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-thiomorpholin-4-yl-piperidin-1-yl]-methanone and potassium peroxymonosulfate (Oxone).

Example 95

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(3,4-dichloro-phenyl)-4-thiomorpholin-4-yl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 571.0 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-(3,4-dichloro-phenyl)-piperidin-4-one, thiomorpholine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 96

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-methyl-phenyl)-4-thiomorpholin-4-yl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 517.3 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-(4-methyl-phenyl)-piperidin-4-one, thiomorpholine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 97

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(3,4-dichloro-phenyl)-4-(1,1-dioxo-1l 6-thiomorpholin-4-yl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 602.1 ($M^+$), was prepared in accordance with the general method of example 51 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(3,4-dichloro-phenyl)-4-thiomorpholin-4-yl-piperidin-1-yl]-methanone and potassium peroxymonosulfate (Oxone).

Example 98

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-methyl-phenyl)-4-(1,1-dioxo-1l 6-thiomorpholin-4-yl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 549.2 ($M^+$), was prepared in accordance with the general method of example 51 from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-methyl-phenyl)-4-thiomorpholin-4-yl-piperidin-1-yl]-methanone and potassium peroxymonosulfate (Oxone).

Example 99

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[4-(2,6-dimethyl-morpholin-4-yl)-3-p-tolyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 529.3 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-(4-methyl-phenyl)-piperidin-4-one, cis-2,6-dimethyl-morpholine and 3,5-bistrifluoromethyl-benzoyl chloride.

Example 100

(-)-(1-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-p-tolyl-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone

Rac-cis-(1-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-p-tolyl-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone (prepared in accordance with the general method of example 32 from 1-benzyl-3-(4-methyl-phenyl)-piperidin-4-one, piperazine and 3,5-bistrifluoromethyl-benzoyl chloride) was separated on chiralpac AD with 10% isopropanol in heptane. The first fraction contained the more active enantiomer, $[\alpha]_{589}^{20} = -6.63$, $[\alpha]_{546}^{20} = -8.10$, $[\alpha]_{436}^{20} = -22.10$, $[\alpha]_{365}^{20} = -61.87$ (c = 0.1358, methanol).

Example 101

(-)-4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazine-1-carboxylic acid tert-butyl ester

Rac-cis-4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazine-1-carboxylic acid tert-butyl ester (prepared from rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone and di-tert.-butyl-carbonat) was separated on chiralpac AD with 6% isopropanol in heptane. The first fraction contained the more active enantiomer, $[\alpha]_{589}^{20} = -2.23$ (c = 0.6740, chloroform).

Example 102

(-)-4-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropylmethyl-piperazin-1-yl)-3-p-tolyl-piperidin-1-yl]-methanone

(-)-(1-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-p-tolyl-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone (245 mg, 0.411 mmol) was dissolved in methanol (1.5 mL). Water (0.15 mL) and potassium carbonate (170 mg, 123 mmol) were added and the reaction mixture was stirred at room temperature for 3 hours. Water (10 mL) was added and the mixture was extracted three times with 20 mL dichloromethane. Organic phases were pooled, dried with magnesium sulfate and evaporated.

The intermediate free piperazine was dissolved in N,N-dimethylformamide (10 mL) and potassium carbonate (166 mg, 1.20 mmol) and bromomethylcyclopropane (0.043 mL, 0.440 mmol) were added at room temperature. The reaction mixture was stirred at room temperature for 3 hours. Water (30 mL) was added and the mixture was extracted three times with 50 mL tert-butyl methylether. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with cyclohexane/ethyl acetate/triethylamine 30:10:1 gave the title compound (171 mg, 77%) as an off-white solid, MS: m/e = 554.3 ($M+H^+$), $[\alpha]_{589}^{20}$ = -19.81 (c = 0.4089, chloroform).

Example 103

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-3-p-tolyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 568.3 ($M+H^+$), $[\alpha]_{589}^{20}$ = -6.48 (c = 0.4012, chloroform), was prepared in accordance with the general method of example 102 (part1) and example 38 from (-)-(1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-p-tolyl-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone and cyclopropyl carbonyl chloride.

Example 104

(-)-(3,5-Bis-trifluoromethyl-phenyl)-{4-[4-(morpholine-4-carbonyl)-piperazin-1-yl]-3-p-tolyl-piperidin-1-yl}-methanone

The title compound, MS: m/e = 613.2 ($M+H^+$), $[\alpha]_{589}^{20}$ = -10.99 (c = 0.4369, chloroform), was prepared in accordance with the general method of example 102 (part1) and example 38 from (-)-(1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-p-tolyl-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone and 4-morpholine carbonyl chloride.

Example 105

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-methanesulfonyl-piperazin-1-yl)-3-p-tolyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 578.1 ($M+H^+$), $[\alpha]_{589}^{20}$ = -19.14 (c = 0.4545, chloroform), was prepared in accordance with the general method of example 102 (part1) and example 38 from (-)-(1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-p-tolyl-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone and methane sulfonyl chloride.

## Example 106

Rac-cis-1-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone

To a mixture of 1-benzyl-3-(4-chloro-phenyl)-piperidin-4-one (15.2 g, 38.5 mmol) and piperazine (6.78 g, 77.1 mmol) in ethanol (6 mL) was added tetraisopropyl-orthotitanate (22.8 mL, 77.1 mmol) at room temperature. After stirring at room temperature for 3 days the reaction mixture was diluted with ethanol (250 mL) and sodium cyanoborohydride (5.10 g, 77.1 mmol) was added. The reaction mixture was stirred at room temperature for 24 h and was diluted with water (30 mL). The inorganic precipitate was filtered off and washed with ethanol and dichloromethane. The solvent was evaporated and the residue was taken up in ethylenglycol (100 mL) and sodium hydroxide (3.08 g, 77.1 mmol) was added. The reaction mixture was stirred at 130°C for 15 min. After cooling water (200 mL) was added and the mixture was extracted four times with 200 mL tert.-butyl methyl ether. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with methylene chloride/methanol/triethyl amine 98:1:1 gave rac-cis-1-[1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazine (9.54 g, 67%) as a yellow oil, MS: m/e = 336.3 ($M+H^+$).

Rac-cis-1-[1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazine (2.00 g, 5.41 mmol) was dissolved in dichloromethane (130 mL) and 9-fluorenylmethyl-chloroformate (1.71 g, 6.49 mmol) in dichloromethane (50 mL) was added at 0°C. The reaction mixture was stirred at room temperature overnight and diluted with sat sodium bicarbonate solution (100 mL). The organic phase was separated and the aqueous layer was extracted twice with 150 mL dichloromethane. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with cyclohexane/ethyl acetate 6:1 gave rac-cis-4-[1-benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (1.75 g, 55%) as a light yellow solid, MS: m/e = 592.3 ($M^+$).

Rac-cis-4-[1-Benzyl-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (1.68 g, 2.84 mmol) was dissolved in toluene (60 mL) and 1-chloroethyl-chloroformate (0.348 mL, 3.13 mmol) were added. The reaction mixture was refluxed overnight. Methanol (55 mL) was added and reflux was continued for 4h. The solvents were evaporated. The crude intermediate was dissolved in dichloromethane (50

mL) and triethylamine (1.99 mL, 14.2 mmol) and 3,5-bistrifluoromethyl-benzoyl chloride (0.643 mL, 3.55 mmol) were added. The reaction mixture was stirred at room temperature overnight and than diluted with 50 mL water. The organic phase was separated and the aqueous layer was extracted twice with 50 mL dichloromethane. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with cyclohexane/ethyl acetate 1:1 gave rac-cis-4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (1.84 g, 87%) as an off-white solid, MS: m/e = 742.3 ($M+H^+$).

Rac-cis-4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (1.79 g, 2.42 mmol) was dissolved in dichloromethane (24 mL). Piperidine (2.4 mL) was added and the reaction mixture was stirred at room temperature overnight. The solvent and the piperidine were evaporated. The crude intermediate was dissolved in dichloromethane (25 mL). 4-Dimethylamino-pyridine (6 mg, 0.05 mmol), pyridine (0.488 mL, 6.04 mmol) and trifluoroacetic acid anhydride (2.6 mL, 18.2 mmol) were added. The reaction mixture was stirred at room temperature overnight and than diluted with 1N sodium hydroxide solution (25 mL). The organic phase was separated and the aqueous layer was extracted twice with 50 mL dichloromethane. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with cyclohexane/ethyl acetate 1:2 gave rac-cis-1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone (730 mg, 49%) as an off-white solid, MS: m/e = 616.2 ($M+H^+$).

## Example 107

Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-dimethylamino-[1,4']bipiperidinyl-1'-yl]-methanone

To a 2 M solution of dimethylamine in methanol (0.38 mL, 0.75 mmol) was added titanium(IV) isopropoxide (0.11 mL, 0.38 mmol) at room temperature. After 10 min. a solution of 1'-(3,5-bis-trifluoromethyl-benzoyl)-3'-(4-chloro-phenyl)-[1,4']bipiperidinyl-4-one (0.10 g, 0.19 mmol) in 1 mL methanol was added to the resulting suspension. The reaction mixture was stirred at room temperature for 5 h. Sodium borohydride (7.0 mg, 0.19 mmol) was added, and stirring at room temperature was continued over night. After quenching with water (0.5 mL) and dilution with methanol (1 ml) the suspension was filtered. The filtrate was concentrated and the resulting slurry triturated with several batches of dichloromethane. The combined organic layers were concentrated. Flash column chromatography afforded the title compound as an off-white solid (58 mg, 55%), MS: m/e = 562 ($M+H^+$).

Example 108

(-)-1-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone

Rac-cis-1-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone was separated on chiralpac AD with 8% isopropanol in heptane. The first fraction contained the more active enantiomer, $[\alpha]_{589}^{20}$ = -19.32 (c = 0.5020, chloroform).

Example 109

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-morpholin-4-yl-[1,4']bipiperidinyl-1'-yl]-methanone

To a solution of morpholine (0.065 mL, 0.75 mmol) in 1 mL methanol was added titanium(IV) isopropoxide (0.11 mL, 0.38 mmol) at room temperature. After 20 min. 1'-(3,5-bis-trifluoromethyl-benzoyl)-3'-(4-chloro-phenyl)-[1,4']bipiperidinyl-4-one (0.10 g, 0.19 mmol) was added to the resulting suspension. The reaction mixture was stirred at room temperature for 5 h. Sodium borohydride (7.0 mg, 0.19 mmol) was added, and stirring at room temperature was continued over night. After quenching with water (0.5 mL) the suspension was triturated with several batches of dichloromethane. The combined organic layers were filtered and concentrated. Flash column chromatography afforded the title compound as a white solid (72 mg, 64%), MS: m/e = 604 ($M+H^+$).

Example 110

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropyl-piperazin-1-yl)-3-p-tolyl-piperidin-1-yl]-methanone

(-)-(1-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-p-tolyl-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone (245 mg, 0.411 mmol) was dissolved in methanol (1.5 mL). Water (0.15 mL) and potassium carbonate (170 mg, 123 mmol) were added and the reaction mixture was stirred at room temperature for 3 hours. Water (10 mL) was added and the mixture was extracted three times with 20 mL dichloromethane. Organic phases were pooled, dried with magnesium sulfate and evaporated.

The intermediate free piperazine was dissolved in methanol (10 mL) and acetic acid (0.109 mL, 1.90 mmol), powdered molecular sieves (1 small spatula), [(1-ethoxycyclopropyl)oxy]trimethylsilane (0.152 mL, 0.761 mmol) and sodium cyanoborohydride (36 mg, 0.571 mmol) were added. The reaction mixture refluxed for 8 hours, cooled and filtered. 2N Sodium hydroxide solution (20 mL) was added to the filtrate

and the mixture was extracted three times with 50 mL ethyl acetate. Organic phases were pooled, dried with magnesium sulfate and evaporated. Chromatography on silica gel with dichloromethane/triethylamine 99:1 gave the title compound (160 mg, 72%) as a white foam, MS: m/e = 540.3 ($M+H^+$), $[\alpha]_{589}^{20}$ = -11.02, $[\alpha]_{546}^{20}$ = -13.78, $[\alpha]_{436}^{20}$ = -36.66, $[\alpha]_{365}^{20}$ = -94.73 (c = 0.4719, chloroform).

Example 111

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-methyl-piperazin-1-yl)-3-p-tolyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 514.4 ($M+H^+$), $[\alpha]_{589}^{20}$ = -25.92, $[\alpha]_{546}^{20}$ = -32.60, $[\alpha]_{436}^{20}$ = -71.06, $[\alpha]_{365}^{20}$ = -152.15 (c = 0.1196, chloroform), was prepared in accordance with the general method of example 102 from (-)-(1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-p-tolyl-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone and methyl iodide.

Example 112

Rac-cis-(3,5-Bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-cyclopropylamino-[1,4']bipiperidinyl-1'-yl]-methanone

To a solution of cyclopropyl amine (0.014 mL, 0.21 mmol), 1'-(3,5-bis-trifluoromethyl-benzoyl)-3'-(4-chloro-phenyl)-[1,4']bipiperidinyl-4-one (0.10 g, 0.19 mmol) and 1 drop of a concentrated aqueous solution of hydrochloric acid in 2 mL ethanol was heated at reflux for two hours. After cooling to 0 °C sodium borohydride (9.0 mg, 0.23 mmol) was added. The reaction mixture was allowed to warm to room temperature over night. After quenching with water (0.5 mL) the mixture was concentrated. Dissolution of the residue in dichloromethane was followed by washing with three portions of water, drying with sodium sulfate and concentration. Flash column chromatography afforded the title compound as a white solid (22 mg, 21%), MS: m/e = 574 ($M+H^+$).

Example 113

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-(4-cyclopropylmethyl-piperazin-1-yl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 574.1 ($M+H^+$), $[\alpha]_{589}^{20}$ = -18.46, $[\alpha]_{546}^{20}$ = -27.04, (c = 0.3846, chloroform), was prepared in accordance with the general method of example 102 from (-)-1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone and cyclopropylmethylbromide.

Example 114

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropylmethyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone

(-)-4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazine-1-carboxylic acid tert-butyl ester (244 mg, 0.417 mmol) was dissolved in dichloromethane (10 mL). Trifluoroacetic acid (0.638 mL, 8.33 mmol) was added and the reaction mixture was stirred at room temperature for 3 hours. Saturated sodium bicarbonate solution was added until pH 8 and the mixture was extracted three times with 30 mL dichloromethane. Organic phases were pooled, dried with magnesium sulfate and evaporated.

The intermediate free piperazine was dissolved in N,N-dimethylformamide (10 mL) and potassium carbonate (166 mg, 1.20 mmol) and bromomethylcyclopropane (0.043 mL, 0.440 mmol) were added at room temperature. The reaction mixture was stirred at room temperature for 3 hours. Water (30 mL) was added and the mixture was extracted three times with 50 mL tert-butyl methylether. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with cyclohexane/ethyl acetate/triethylamine 20:10:1 gave the title compound (100 mg, 44%) as a white solid, MS: m/e = 540.3 ($M+H^+$), $[\alpha]_{589}^{20}$ = -7.80, $[\alpha]_{546}^{20}$ = -9.69, $[\alpha]_{436}^{20}$ = -28.60, $[\alpha]_{365}^{20}$ = -78.71 (c = 0.4231, chloroform).

Example 115

(-)-(3,5-Bis-trifluoromethyl-phenyl)-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-3-phenyl-piperidin-1-yl}-methanone

The title compound, MS: m/e = 530.3 ($M+H^+$), $[\alpha]_{589}^{20}$ = -8.02, $[\alpha]_{546}^{20}$ = -5.61, $[\alpha]_{436}^{20}$ = -20.05, $[\alpha]_{365}^{20}$ = -59.35 (c = 0.1247, chloroform), was prepared in accordance with the general method of example 114 from (-)-4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazine-1-carboxylic acid tert-butyl ester and 2-amino ethanol.

Example 116

Rac-cis-(3,5-Dichloro-phenyl)-[4-(4-methyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 432.2 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-phenyl-piperidin-4-one, N-methyl-piperazine and 3,5-dichloro-benzoyl chloride.

Example 117

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-phenyl-piperazin-1-yl)-3-p-tolyl-piperidin-1-yl]-methanone

(-)-(1-{4-[1-(3,5-Bis-trifluoromethyl-benzoyl)-3-p-tolyl-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone (245 mg, 0.411 mmol) was dissolved in methanol (1.5 mL). Water (0.15 mL) and potassium carbonate (170 mg, 123 mmol) were added and the reaction mixture was stirred at room temperature for 3 hours. Water (10 mL) was added and the mixture was extracted three times with 20 mL dichloromethane. Organic phases were pooled, dried with magnesium sulfate and evaporated.

The intermediate free piperazine was dissolved in toluene (5 mL) and bromobenzene (0.084 mL, 0.80 mmol), sodium tert.-butylate (54 mg, 0.561 mmol), tris(dibenzylidenaceton)dipalladium (4 mg, 0.004 mmol) and rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (5 mg, 0.008 mmol) were added. The reaction mixture was strirred at 80°C overnight. Water (20 mL) was added and the mixture was extracted three times with 20 mL ethyl acetate. Organic phases were pooled, dried with magnesium sulfate and evaporated. Chromatography on silica gel with dichloromethane/triethylamine 99:1 gave the title compound (128 mg, 54%) as an yellow oil, MS: m/e = 576.1 ($M+H^+$), $[\alpha]_{589}^{20}$ = -10.62, $[\alpha]_{546}^{20}$ = -9.66, $[\alpha]_{436}^{20}$ = -20.28 (c = 0.1035, chloroform).

Example 118

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-[4-(3-Amino-pyrrolidin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone

The title compound, MS: m/e = 504.3 ($M+H^+$), was prepared in accordance with the general method of example 77, step 1-3, from (3R,3'R,4S)- and (3S,3'R,4R)-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-(3-hydroxy-pyrrolidin-1-yl)-piperidin-1-yl]-methanone. The 3'-stereogenic center racemized under the reaction conditions.

Example 119

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 526.2 ($M+H^+$), $[\alpha]_{589}^{20}$ = -6.17, $[\alpha]_{436}^{20}$ = -23.81, $[\alpha]_{365}^{20}$ = -74.09 (c = 0.1134, chloroform), was prepared in accordance with the general method of example 114 (step1) and example 110 (step 2) from (3S,4R) or (3R,4S)-4-[1-(3,5-bis-

trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazine-1-carboxylic acid tert-butyl ester and [(1-ethoxycyclopropyl)-oxy]trimethylsilane.

Example 120

Rac-cis-(3,5-Difluoro-phenyl)-[4-(4-methyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 400.5 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-phenyl-piperidin-4-one, N-methyl-piperazine and 3,5-difluoro-benzoyl chloride.

Example 121

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-[Cyclopropanecarboxylic acid {1-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-fluoro-phenyl)-piperidin-4-yl]-pyrrolidin-3-yl}-amide

The title compound, MS: m/e = 572.2 ($M+H^+$), was prepared in accordance with the general method of example 38 from (3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-[4-(3-amino-pyrrolidin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone and cyclopropane carboxylic acid chloride.

Example 122

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-[Cyclopropanecarboxylic acid {1-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-fluoro-phenyl)-piperidin-4-yl]-pyrrolidin-3-yl}-methyl-amide

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-[Cyclopropanecarboxylic acid {1-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-fluoro-phenyl)-piperidin-4-yl]-pyrrolidin-3-yl}-amide (155 mg, 0.271 mmol) was dissolved in N,N-dimethylforamide (5 mL). Sodium hydride (17 mg, 55% in mineral oil, 0.407 mmol) and methyl iodide (0.021 mL, 0.339 mmol) were added and the reaction mixture was stirred at room temperature overnight. Water (30 mL) was added and the mixture was extracted three times with 50 mL tert.-butyl methyl ether. Organic phases were pooled, dried with magnesium sulfate and evaporated. Chromatography on silica gel with methylen chloride/triethyl amine 99:1 gave the desired product (30 mg, 19%) as a colorless oil, MS: m/e = 586.2 ($M+H^+$).

Example 123

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-(3,5-Bis-trifluoromethyl-phenyl)-[4-(3-dicyclopropylamino-pyrrolidin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 584.3 $(M+H)^+$, was prepared in accordance with the general method of example 110 (step 2) from (3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-[4-(3-amino-pyrrolidin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone and [(1-ethoxycyclopropyl)-oxy]trimethylsilane.

Example 124

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-[4-[3-(Bis-cyclopropylmethyl-amino)-pyrrolidin-1-yl]-3-(4-fluoro-phenyl)-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone

The title compound, MS: m/e = 612.2 $(M+H)^+$, was prepared in accordance with the general method of example 35 from (3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-[4-(3-amino-pyrrolidin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone and bromomethyl cyclopropane.

Example 125

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-(3,5-Bis-trifluoromethyl-phenyl)-[4-(3-dimethylamino-pyrrolidin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-methanone

(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-[4-(3-Amino-pyrrolidin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone (200 mg, 0.397 mmol) was dissolved in formic acid (2 mL) and formaldehyd (0.094 mL, 36% solution in water, 1.19 mmol) was added. The reaction mixture was stirred at 110°C overnight. Saturated sodium bicarbonate solution was added until pH 9 and the mixture was extracted three times with 50 mL ethyl acetate. Organic phases were pooled, dried with magnesium sulfate and evaporated. Flash chromatography on silica gel with methanol in methylen chloride (0% - 10% gradient) gave the title product (150 mg, 71%) as an off-white foam, MS: m/e = 532.2 $(M+H^+)$.

Example 126

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-3-(4-chloro-phenyl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 588.2 $(M+H^+)$, $[\alpha]_{589}^{20}$ = -16.03, $[\alpha]_{546}^{20}$ = -20.15, $[\alpha]_{436}^{20}$ = -45.28, $[\alpha]_{365}^{20}$ = -102.27 (c = 0.4615, chloroform), was prepared in accordance with the general method of example 102 (part1) and example 38 from (-)-(1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone and cyclopropyl carbonyl chloride.

Example 127

(+)-(3,5-Dichloro-phenyl)-[4-(4-methyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone

Rac-cis-(3,5-Dichloro-phenyl)-[4-(4-methyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone was separated on chiralpac AD with 10% isopropanol in heptane. The first fraction contained the more active enantiomer, $[\alpha]_{589}^{20} = +23.46$, $[\alpha]_{546}^{20} = +27.81$, $[\alpha]_{436}^{20} = +39.10$, $[\alpha]_{365}^{20} = +38.23$ (c = 0.1151, methanol).

Example 128

Rac-cis-(3-Fluoro-5-trifluoromethyl-phenyl)-[4-(4-methyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone

The title compound, MS: m/e = 450.5 ($M+H^+$), was prepared in accordance with the general method of example 26 from 1-benzyl-3-phenyl-piperidin-4-one, N-methyl-piperazine and 3-fluoro-5-trifluoromethyl-benzoyl chloride.

Example 129

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 534.3 ($M+H^+$), $[\alpha]_{589}^{20} = -53.04$, $[\alpha]_{546}^{20} = -65.78$, $[\alpha]_{436}^{20} = -135.72$, $[\alpha]_{365}^{20} = -277.94$ (c = 0.3846, chloroform), was prepared in accordance with the general methods of example 102 (part1) and example 125 from (-)-(1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone and formaldehyde.

Example 130

(-)-(3,5-Bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-(4-cyclopropyl-piperazin-1-yl)-piperidin-1-yl]-methanone

The title compound, MS: m/e = 560.2 ($M+H^+$), $[\alpha]_{589}^{20} = -24.38$, $[\alpha]_{546}^{20} = -30.39$, $[\alpha]_{436}^{20} = -64.51$ (c = 0.6154, chloroform), was prepared in accordance with the general methods of example 102 (step1) and example 110 (step2) from (-)-(1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone and [(1-ethoxycyclopropyl)-oxy]trimethylsilane.

Example A

Tablets of the following composition are manufactured in the usual manner:

| | mg/tablet |
|---|---|
| Active substance | 5 |
| Lactose | 45 |
| Corn starch | 15 |
| Microcrystalline cellulose | 34 |
| Magnesium stearate | 1 |
| Tablet weight | 100 |

Example B

Capsules of the following composition are manufactured:

| | mg/capsule |
|---|---|
| Active substance | 10 |
| Lactose | 155 |
| Corn starch | 30 |
| Talc | 5 |
| Capsule fill weight | 200 |

The active substance, lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer, the talc is added thereto and mixed thoroughly. The mixture is filled by machine into hard gelatine capsules.

Example C

Suppositories of the following composition are manufactured:

| | | mg/supp. |
|---|---|---|
| Active substance | | 15 |
| Suppository mass | | 1285 |
| | Total | 1300 |

The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45°C. Thereupon, the finely powdered active substance is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of suitable size, left to cool, the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

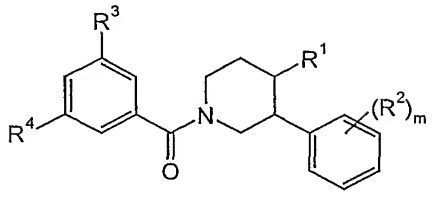
Example D

An injection solution may have the following composition and is manufactured in usual manner:

| | |
|---|---|
| Active substance | 1.0 mg |
| 1 n HCl | 20.0 µl |
| acetic acid | 0.5 mg |
| NaCl | 8.0 mg |
| phenol | 10.0 mg |
| 1 n NaOH | q.s. ad pH 5 |
| $H_2O$ | q.s. ad 1 ml |

## Claims

1. Compounds of the general formula



I

wherein

$R^1$ a) is phenyl, unsubstituted or substituted by one or more substituents selected from the group $R^{1'}$ consisting of
- halogen,
- trifluoromethyl,
- piperazinyl, optionally substituted by lower alkyl,
- morpholinyl,
- NH-phenyl,
- pyrrolidinyl,
- $NH(CH_2)_n$-O-lower alkyl,
- $NR_2$,
- $NH(CH_2)_n$-cycloalkyl,
- $NH(CH_2)_n$-$NR_2$, or is

b) morpholinyl, optionally substituted by one or two lower alkyl groups, or is

c) piperazinyl, unsubstituted or substituted in the 4-position by the group $R^{1''}$ which is
- lower alkyl,
- cycloalkyl,
- phenyl,
- benzoxazolyl,
- pyridinyl,
- pyrimidinyl
- pyrazinyl,
- $(CH_2)_n$-cycloalkyl,
- $(CH_2)_n$-phenyl,
- $(CH_2)_n$-hydroxy,
- $(CH_2)_n$-$CF_3$,

- $(CH_2)_n$-C(O)-morpholinyl,
- $(CH_2)_n$-C(O)-N(R)-phenyl, wherein the phenyl ring is optionally substituted by lower alkyl or halogen,
- $(CH_2)_n$-C(O)-$NR_2$,
- C(O)-phenyl, wherein the phenyl ring is optionally substituted by trifluoromethyl,
- C(O)-$(CH_2)_n$-phenyl,
- C(O)-$NR_2$,
- C(O)-NR-$(CHR)_n$-phenyl,
- C(O)-lower alkyl,
- C(O)-$CF_3$,
- C(O)-cycloalkyl,
- C(O)-morpholinyl,
- C(O)O-lower alkyl,
- C(O)-O-$(CH_2)_n$-$NR_2$,
- $S(O)_2$-lower alkyl,

or is

d) pyrrolidinyl, optionally substituted by one or more groups $R^{1'''}$, which are

- halogen,
- hydroxy,
- =O,
- $NR_2$,
- N(cycloalkyl)$_2$,
- N[$(CH_2)_n$cycloalkyl]$_2$,
- NR-C(O)-cycloalkyl,
- O-$(CH_2)_n$-cycloalkyl; or is

e) piperidinyl, optionally sbstituted by one or more groups $R^{1''''}$ in the 3 or 4-position, which groups are

- hydroxy,
- =O,
- halogen,
- morpholinyl,
- $NR_2$,
- NR-cycloalkyl,
- NR-C(O)-cycloalkyl,
- NR-C(O)-phenyl,
- NR-C(O)-$(CH_2)_n$-phenyl,
- O-$(CH_2)_n$-cycloalkyl,

or is

f) thiomorpholinyl, 1-oxo-thiomorpholinyl or 1,1-dioxothiomorpholinyl;

$R^2$ is independently from "m" hydrogen, halogen, lower alkyl, -NH-$(CH_2)_n$-O-lower alkyl, pyrrolidinyl or morpholinyl;

$R^3/R^4$ are independently from each other trifluoromethyl or halogen;

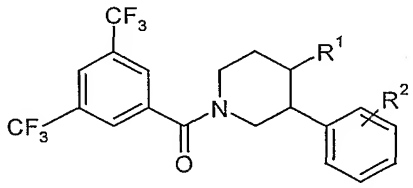
R is hydrogen or lower alkyl and may be the same or different in case of $R_2$;

n is 1, 2, 3 or 4;

m is 0, 1 or 2;

and to pharmaceutically acceptable acid addition salts thereof.

2. *Compounds according to claim 1 having the formula*



I-1

wherein

$R^1$ is phenyl, unsubstituted or substituted by one or two substituents, selected from the group $R^{1'}$, consisting of

- halogen,
- trifluoromethyl,
- piperazinyl, optionally substituted by lower alkyl,
- morpholinyl,
- NH-phenyl,
- pyrrolidinyl,
- $NH(CH_2)_n$-O-lower alkyl,
- $NR_2$,
- $NH(CH_2)_n$-cycloalkyl,
- $NH(CH_2)_n$-$NR_2$, or is

morpholinyl, or is

piperazinyl, unsubstituted or substituted by the group $R^{1''}$, which is

- lower alkyl,
- cycloalkyl,

- C(O)-phenyl, wherein the phenyl ring is optionally substituted by trifluoromethyl,
- $(CH_2)_n$-C(O)-$NR_2$,
- $(CH_2)_n$-cycloalkyl,
- $(CH_2)_n$-phenyl,
- C(O)-lower alkyl,
- C(O)-$CF_3$,
- C(O)-cycloalkyl,
- C(O)-morpholinyl,
- C(O)-O-$(CH_2)_n$-$NR_2$,
- $(CH_2)_n$-C(O)-N(R)-phenyl, wherein the phenyl ring is optionally substituted by lower alkyl,
- pyrazinyl, or is

pyrrolidinyl, optionally substituted by the group $R^{1'''}$, which is
- hydroxy,
- =O,
- O-$(CH_2)_n$-cycloalkyl, or is

piperidinyl, optionally sbstituted by the group $R^{1''''}$, which is
- hydroxy,
- O-$(CH_2)_n$-cycloalkyl,
- =O,
- halogen, or is

thiomorpholinyl, 1-oxo-thiomorpholinyl or 1,1-dioxothiomorpholinyl;

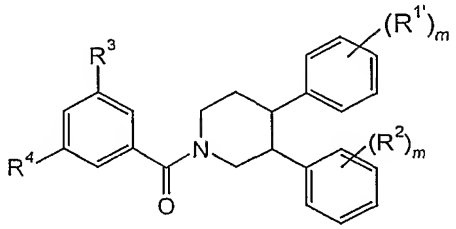
$R^2$ is hydrogen, halogen, lower alkyl, -NH-$(CH_2)_n$-O-lower alkyl, pyrrolidinyl or morholinyl;

R is hydrogen or lower alkyl and may be the same or different in case of $R_2$; and

n is 1, 2, 3 or 4;

and pharmaceutically acceptable acid addition salts thereof.

3. Compounds according to claim 1 or 2 having the formula




1A,

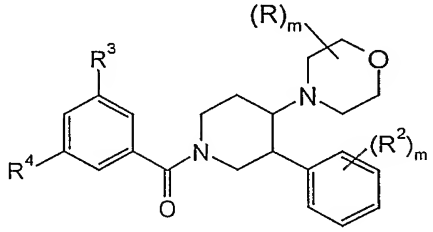
wherein m is 0, 1 or 2 and $R^{1'}$, $R^2$, $R^3$ and $R^4$ are described in claim 1 or 2.

4. Compounds of formula 1A in accordance with claim 3, in which $R^{1'}$ is hydrogen, bromo, morpholinyl, 4-methyl-piperazinyl or $-NH(CH_2)_2OCH_3$ and $R^2$ is described in claim 1.

5. Compounds of formula 1A in accordance with claim 4, which are

rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-morpholin-4-yl-phenyl)-3-phenyl-piperidin-1-yl]-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-{4-[4-(4-methyl-piperazin-1-yl)-phenyl]-3-phenyl-piperidin-1-yl}-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-phenyl-piperidin-1-yl]-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(3-bromo-phenyl)-3-phenyl-piperidin-1-yl]-methanone or
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-{4-[4-(2-methoxy-ethylamino)-phenyl]-3-phenyl-piperidin-1-yl}-methanone.

6. Compounds of formula IB according to claim 1 or 2 having the formula



IB,

wherein R is lower alkyl, m is 0, 1 or 2, $R^2$, $R^3$ and $R^4$ have the significances given in claims 1 or 2.

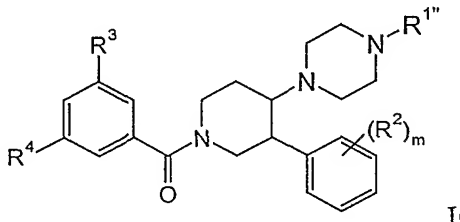
7. Compounds of formula 1B in accordance with claim 6, in which $R^2$ is hydrogen, fluoro or chloro.

8. Compounds of formula 1B in accordance with claim 7, which are

rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-morpholin-4-yl-piperidin-1-yl]-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(4-morpholin-4-yl-3-phenyl-piperidin-1-yl)-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-morpholin-4-yl-piperidin-1-yl]-methanone or

Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-morpholin-4-yl-[1,4']bipiperidinyl-1'-yl]-methanone.

9. Compounds of formula IC according to claim 1 or 2 having the formula



IC,

wherein m is 0, 1 or 2, $R^{1"}$, $R^2$, $R^3$ and $R^4$ have the significances given in claim 1 or 2.

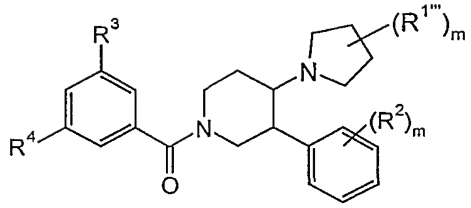
10. Compounds of formula IC in accordance with claim 9, wherein $R^{1"}$ is hydrogen, methyl, $-C(O)CF_3$, $-(CH_2)_2OH$, $-CH_2C(O)N(CH_3)_2$, $CH_2$-cyclopropyl, benzyl, -C(O)-cyclopropyl, -C(O)-morpholinyl, pyrazinyl, cyclopropyl or $-CH_2CONHC_6H_3(CH_3)_2$, $-CH_2CONHC_6H_4F$, $-C(O)CH_2$-phenyl, and $R_2$ is hydrogen, methyl, chloro or fluoro.

11. Compounds of formula 1C in accordance with claim 10, which are

rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-methyl-piperazin-1-yl), -3-phenyl-piperidin-1-yl]-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-piperazin-1-yl-piperidin-1-yl)-methanone,
rac-cis-2 {4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-N,N-dimethyl-acetamide,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropylmethyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone,
rac-cis-[4-(4-benzyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone,
rac-cis-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-morpholin-4-yl-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone,
rac-cis-2-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-N-(2,6-dimethyl-phenyl)-acetamide,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-phenyl-4-(2,3,5,6-tetrahydro-

[1,2']bipyrazinyl-4-yl)-piperidin-1-yl]-methanone,
(+)-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone,
Rac-cis-2-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-N-(4-fluoro-phenyl)-acetamide,
Rac-cis-1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-piperazin-1-yl}-2-phenyl-ethanone,
Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-piperazin-1-yl-piperidin-1-yl]-methanone,
Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropylmethyl-piperazin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-fluoro-phenyl)-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[3-phenyl-4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-methanone,
(-)-4-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropylmethyl-piperazin-1-yl)-3-p-tolyl-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropanecarbonyl-piperazin-1-yl)-3-p-tolyl-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-{4-[4-(morpholine-4-carbonyl)-piperazin-1-yl]-3-p-tolyl-piperidin-1-yl}-methanone,
Rac-cis-1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone,
(-)-1-{4-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-(4-chloro-phenyl)-piperidin-4-yl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropyl-piperazin-1-yl)-3-p-tolyl-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-methyl-piperazin-1-yl)-3-p-tolyl-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-(4-cyclopropylmethyl-piperazin-1-yl)-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropylmethyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone,
(-)-(3,5-bis-trifluoromethyl-phenyl)-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-3-phenyl-piperidin-1-yl}-methanone or
(-)-(3,5-bis-trifluoromethyl-phenyl)-[4-(4-cyclopropyl-piperazin-1-yl)-3-phenyl-piperidin-1-yl]-methanone.

12. Compounds of formula ID according to claim 1 or 2 having the formula



ID,

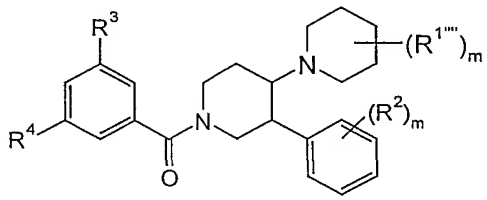
wherein m is 0, 1 or 2, $R^{1'''}$, $R^2$, $R^3$ and $R^4$ have the significances given in claim 1 or 2.

13. Compounds of formula ID in accordance with claim 12, wherein $R^{1'''}$ is hydrogen, hydroxy, amino, -$OCH_2$-cyclopropyl or =O and $R^2$ is hydrogen, chloro or fluoro.

14. Compounds of formula 1D in accordance with claim 13, which are

(3R,3'R,4R)- and (3S,3'R,4S)-(3,5-bis-trifluoromethyl-phenyl)-[4-(3'-hydroxy-pyrrolidin-1'-yl)-3-phenyl-piperidin-1-yl]-methanone,
(3R,3'R,4R)- and (3S,3'R,4S)-(3,5-bis-trifluoromethyl-phenyl)-[4-(3-cyclopropylmethoxy-pyrrolidin-1-yl)-3-phenyl-piperidin-1-yl]-methanone,
rac-cis-1-[1-(3,5-bis-trifluoromethyl-benzoyl)-3-phenyl-piperidin-4-yl]-pyrrolidin-3-one,
(-)-(3,5-bis-trifluoromethyl-phenyl)-[3-(4-chloro-phenyl)-4-pyrrolidin-1-yl-piperidin-1-yl]-methanone or
(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-[4-(3-Amino-pyrrolidin-1-yl)-3-(4-fluoro-phenyl)-piperidin-1-yl]-(3,5-bis-trifluoromethyl-phenyl)-methanone.

15. Compounds of formula IE according to claim 1 or 2 having the formula



IE,

wherein m is 0, 1 or 2, $R^{1''''}$, $R^2$, $R^3$ and $R^4$ have the significances given in claims 1 or 2.

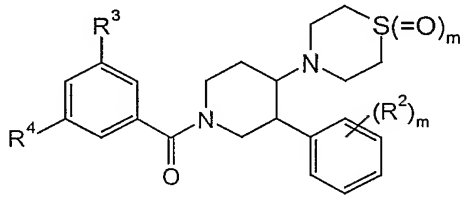
16. Compounds of formula IE in accordance with claim 15, wherein $R^{1''''}$ is fluoro, hydroxy, -NHC(O)-cyclopropyl, -$NHC(O)CH_2$-phenyl, -NH-cyclopropyl,-$N(CH_2)_2$, -$OCH_2$-cyclopropyl or =O and $R^2$ is hydrogen, chloro or fluoro.

17. Compounds of formula 1E in accordance with claim 16, which are

rac-cis- (3,5-bis-trifluoromethyl-phenyl)-(4,4-difluoro-3'-phenyl-[1,4']bipiperidinyl-1'-yl)-methanone,

rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-fluoro-phenyl)-3-hydroxy-[1,4']bipiperidinyl-1'-yl]-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(4-hydroxy-3'-phenyl-[1,4']bipiperidinyl-1'-yl)-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(4-cyclopropylmethoxy-3'-phenyl-[1,4']bipiperidinyl-1'-yl)-methanone,
rac-cis-1'-(3,5-bis-trifluoromethyl-benzoyl)-3'-phenyl-[1,4']bipiperidinyl-4-one,
Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-hydroxy-[1,4']bipiperidinyl-1'-yl]-methanone,
Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-cyclopropylmethoxy-[1,4']bipiperidinyl-1'-yl]-methanone,
(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-cyclopropanecarboxylic acid [1'-(3,5-bis-trifluoromethyl-benzoyl)-3'-(4-fluoro-phenyl)-[1,4']bipiperidinyl-3-yl]-amide,
(3RS,3'RS,4SR)- and (3RS,3'SR,4SR)-N-[1'-(3,5-bis-trifluoromethyl-benzoyl)-3'-(4-fluoro-phenyl)-[1,4']bipiperidinyl-3-yl]-2-phenyl-acetamide,
Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-dimethylamino-[1,4']bipiperidinyl-1'-yl]-methanone or
Rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[3'-(4-chloro-phenyl)-4-cyclopropylamino-[1,4']bipiperidinyl-1'-yl]-methanone.

18. Compounds of formula IF according to claim 1 or 2 having the formula



1F

wherein $R^2$, $R^3$ and $R^4$ are described in claims 1 or 2 and m is 0, 1 or 2.

19. Compounds of formula IF in accordance with claim 18, wherein m is 0, 1 or 2 and $R^2$ is hydrogen.

20. Compounds of formula 1F in accordance with claim 19, which are

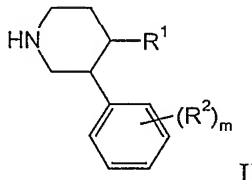
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-(3-phenyl-4-thiomorpholin-4-yl-piperidin-1-yl)-methanone,
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(1-oxo-1l 4-thiomorpholin-4-yl)-3-phenyl-piperidin-1-yl]-methanone or
rac-cis-(3,5-bis-trifluoromethyl-phenyl)-[4-(1,1-dioxo-1l 6-thiomorpholin-4-yl)-3-phenyl-piperidin-1-yl]-methanone.

21. A medicament containing one or more compounds as claimed in any one of claims 1-20 and pharmaceutically acceptable excipients.

22. A medicament according to claim 21 for the treatment of diseases related to NK-1 receptor antagonists.

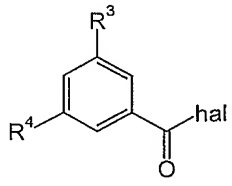
23. A process for preparing a compound of formula I as defined in claim 1, which process comprises

a) reacting a compound of formula



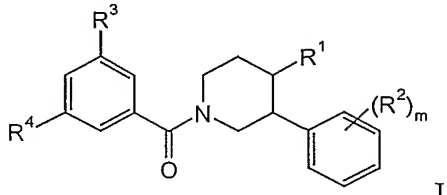
II

with a compound of formula



III

to a compound of formula

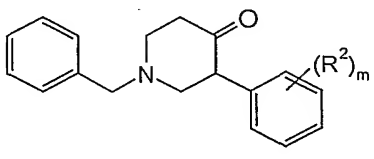


I

wherein $R^1$ is phenyl, optionally substituted by halogen, $R^2$, $R^3$ and $R^4$ have the significances given in claim 1, hal is halogen and m is 0, 1 or 2,

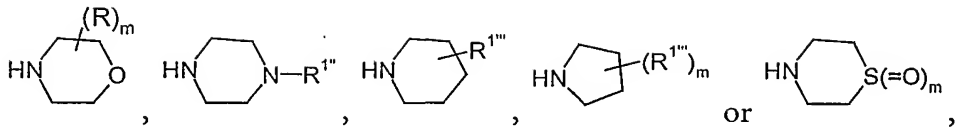
or

b) reacting a compound of formula

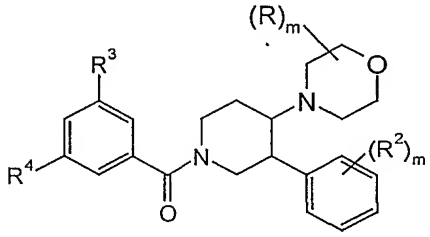


IV

with a compound of formulas

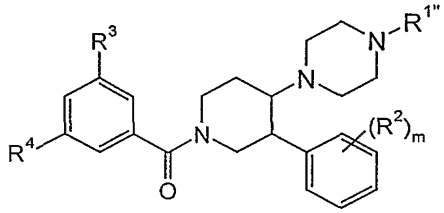


debenzylating, and then acylating with a compound of formula III to give a compound of formulas



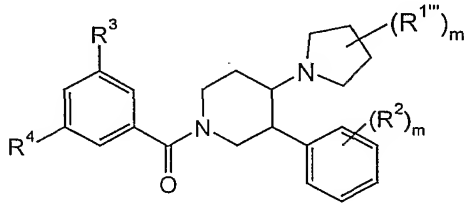
IB,

wherein R, $R^2$, $R^3$, $R^4$ and m have the significances given in claim 1, or



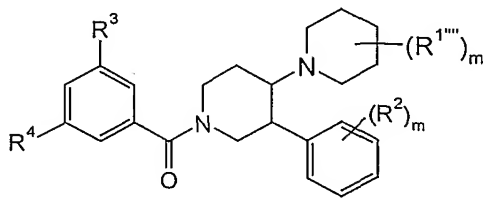
IC,

wherein $R^{1''}$, $R^2$, $R^3$, $R^4$ and m have the significances given in claim 1, or



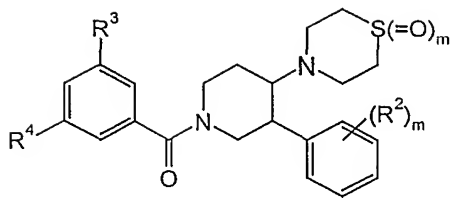
ID,

wherein $R^{1'''}$, $R^2$, $R^3$, $R^4$ and m have the significances given in claim 1, or



IE,

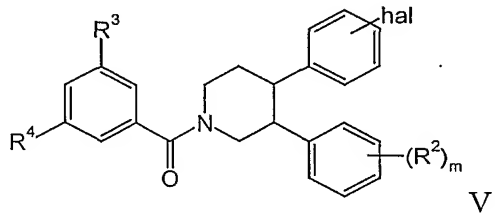
wherein $R^{1''''}$, $R^2$, $R^3$, $R^4$ and m have the significances given in claim 1, or



IF

wherein $R^2$, $R^3$, $R^4$ and m have the significances given in claim 1, or

c) aminating a compound of formula

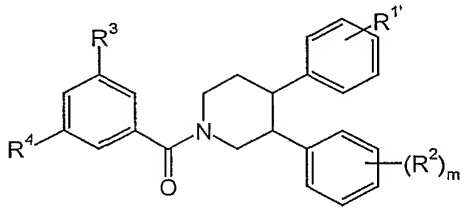


V

with an amine derivative of formula

$R^{1'}H$ VI

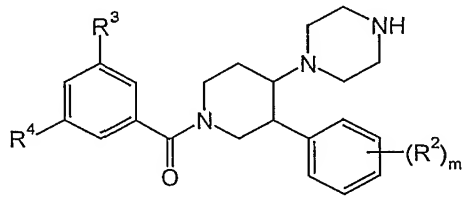
to a compound of formula



IA1

wherein $R^{1'}$ is piperazinyl, optionally substituted by lower alkyl, morpholinyl, -NH-phenyl, pyrrolidinyl, $-NH(CH_2)_n$-O-lower alkyl, $-NR_2$, $-NH(CH_2)_n$-cycloalkyl or $-NH(CH_2)_n-NR_2$, and the definitions of $R^2$, $R^3$ and $R^4$ is given in claim 1, or

d) reacting a compound of formula

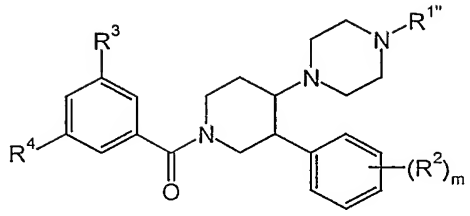


IC1

with a compound of formula

$R^{1"}$hal VII

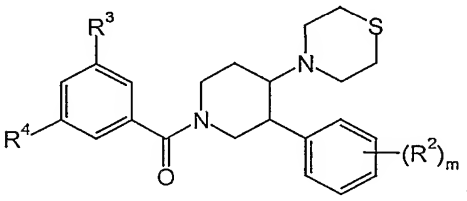
to a compound of formula



IC

wherein the definitions of substituents are given in claim 1, or

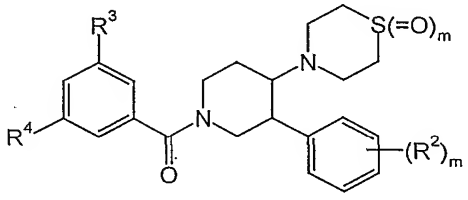
e) oxidizing a compound of formula



IF1

with oxone®

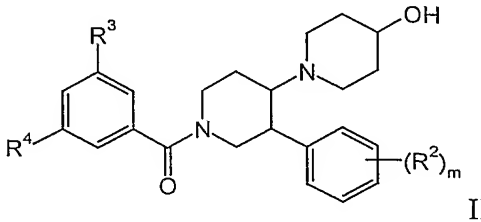
to a compound of formula



IF

wherein m is 1 or 2 and $R^2$, $R^3$ and $R^4$ are described in claim 1, or

f) alkylating a compound of formula

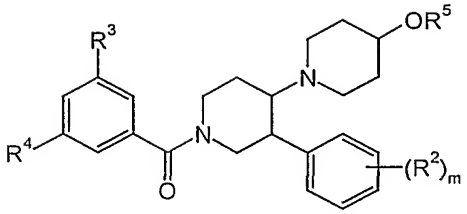


IE1

with a compound of formula

$R^5$hal VIII

to a compound of formula

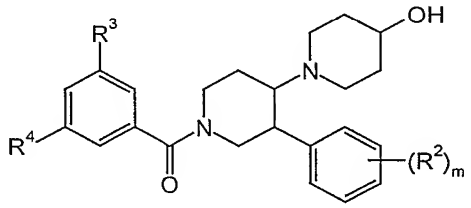


IE2

wherein $R^5$ is $-(CH_2)_n$-cycloalkyl, and $R^2$, $R^3$, $R^4$ and m are described in claim 1, or

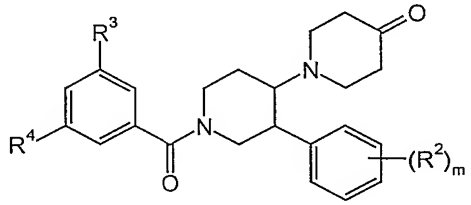
or

g) oxidizing a compound of formula



IE1

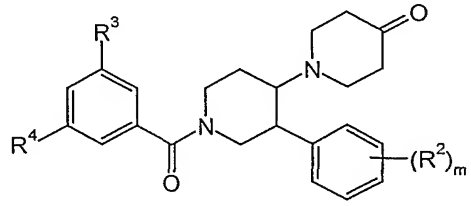
to a compound of formula



IE3

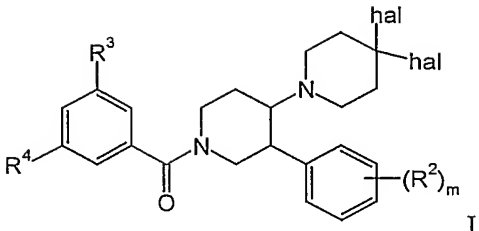
wherein $R^2$, $R^3$, $R^4$ and m are described in claim 1, or

h) halogenating a compound of formula



IE3

to a compound of formula




IE4,

and

if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

24. A compound according to any one of claims 1-20, whenever prepared by a process as claimed in claim 23 or by an equivalent method.

25. The use of a compound in any one of claims 1-20 for the treatment of diseases related to NK-1 receptor antagonists.

26. The use of a compound in any one of claims 1-20 for the manufacture of medicaments containing one or more compounds of formula I for the treatment of diseases related to NK-1 receptor antagonists.

27. The invention as hereinbefore described.

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# INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/00851

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/04 C07D211/14 C07D295/12 A61K31/4545 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, CHEM ABS Data, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| A | WO 00 53572 A (HOFFMANN LA ROCHE)<br>14 September 2000 (2000-09-14)<br>claim 1 | 1-27 |
| A | WO 97 25322 A (PFIZER RES & DEV ;PFIZER LTD (GB); PFIZER (US); MACKENZIE ALEXANDE)<br>17 July 1997 (1997-07-17)<br>claim 1; example 1 | 1-27 |

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 18 April 2002 | 03/05/2002 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Seelmann, I |

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication,where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | KUDLACZ E M ET AL: "THE PERIPHERAL NK-1/NK-2 RECEPTOR ANTAGONIST MDL 105,172A INHIBITS TACHYKININMEDIATED RESPIRATORY EFFECTS IN GUINEA-PIGS" JOURNAL OF AUTONOMIC PHARMACOLOGY, GALEN PRESS, NORTH FERRIBY, GB, vol. 17, no. 2, 2 April 1997 (1997-04-02), pages 109-119, XP002057582 ISSN: 0144-1795 figure 1 --- | 1-27 |
| A | VEENSTRA S J ET AL: "SAR of 2-Benzyl-4-Aminopiperidines NK1 Antagonists. Part 2. Synthesis of CGP 49823" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 24, 17 December 1996 (1996-12-17), pages 3029-3034, XP004135949 ISSN: 0960-894X figure 1 --- | 1-27 |
| A | KOELSCH: "A SYNTHESIS OF 3-PHENYLPIPERIDINES" J. AMER. CHEM. SOC., vol. 65, 1943, pages 2093-2095, XP001069263 page 2095, line 41 - line 45 ----- | 1-27 |

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Information on patent family members

International Application No
PCT/EP 02/00851

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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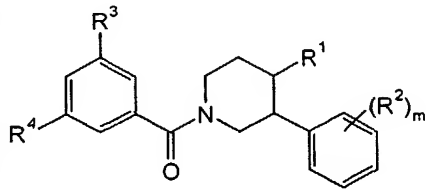


(I)

(57) Abstract: The invention relates to compounds of the general formula, wherein $R^1$ is optionally substituted phenyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl or is thiomorpholinyl, 1-oxo-thiomorpholinyl or 1,1-dioxothiomorpholinyl. These compounds have a good affinity to the NK-1 receptor and they are therefore suitable in the control or treatment of diseases, related to this receptor.